EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 February 2019
EMA/217823/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

angiotensin-II-receptor antagonists (sartans) containing a tetrazole group

Procedure no: EMEA/H/A-31/1471

Nationally authorised products: various

Centrally authorised products:

Amlodipine-Valsartan Mylan EMEA/H/A-31/1471/C/4037/0004; Aprovel EMEA/H/A-31/1471/C/141/0172; Coaprovel EMEA/H/A-31/1471/C/222/0187; Copalia EMEA/H/A-31/1471/C/774/0099; Copalia HCT EMEA/H/A-31/1471/C/1159/0069; Dafiro EMEA/H/A-31/1471/C/776/0101; Dafiro HCT EMEA/H/A-31/1471/C/1160/0070; Entresto EMEA/H/A-31/1471/C/4062/0021; Exforge EMEA/H/A-31/1471/C/716/0098; Exforge HCT EMEA/H/A-31/1471/C/1068/0068; Ifirmacombi EMEA/H/A-31/1471/C/2302/0020; Ifirmasta EMEA/H/A-31/1471/C/962/0018; Irbesartan Hydrochlorothiazide Zentiva EMEA/H/A-31/1471/C/783/0101; Irbesartan Teva EMEA/H/A-31/1471/C/1093/0032; Irbesartan Zentiva EMEA/H/A-31/1471/C/785/0080; Irbesartan/Hydrochlorothiazide Teva EMEA/H/A-31/1471/C/1112/0041; Karvea EMEA/H/A-31/1471/C/142/0175; Karvezide EMEA/H/A-31/1471/C/221/0188; Neparvis EMEA/H/A-31/1471/C/4343/0020

Active substances: candesartan, irbesartan, losartan, olmesartan, valsartan

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

The EU authorities were notified on June 2018 that an Active Pharmaceutical Ingredient (API) manufacturer (Zhejiang Huahai Pharmaceutical, China) has detected the presence of a previously undetected process impurity, *N*-nitrosodimethylamine (NDMA, also known as dimethylnitrosamine) in the valsartan API manufactured at its site in Chuannan. Zhejiang Huahai (ZH) is one of the API manufacturers that are supplying valsartan for medicinal products authorised in the EU.

NDMA is a genotoxic and carcinogenic agent in animals and it is classified as probably carcinogenic to humans (Class 2A carcinogen) by the International Agency for Research on Cancer (IARC, WHO). ZH provided an initial investigation report on the root cause of the presence of NDMA upon request from the supervisory authority in Italy (AIFA). This initial investigation report by the manufacturer indicated that NDMA is formed at the tetrazole ring-forming step in ZH's valsartan API manufacturing process, (which includes quenching of remaining azide with nitrous acid) and the level of NDMA present may depend on the reaction conditions used.

On 5 July 2018 the EC triggered a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of valsartan-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

After the referral procedure started, NDMA was also identified in valsartan from some other API manufacturers, including Zhejiang Tianyu. In addition, further *N*-nitroso impurities were identified in some valsartan batches and in batches of other sartans.

During the CHMP plenary meeting in September 2018, the scope of the referral was widened to include all sartans with a tetrazole moiety in their molecular structure.

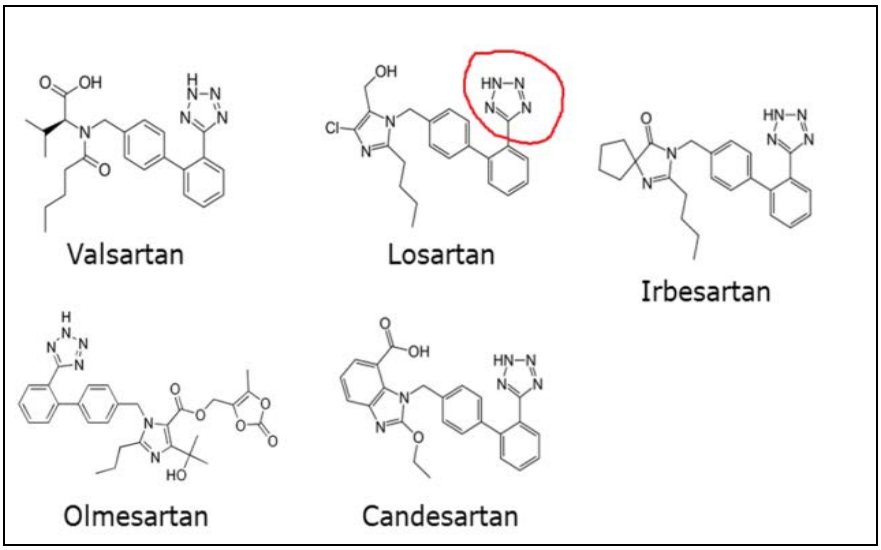
2. Scientific discussion

2.1. Introduction

Angiotensin-II-receptor antagonists/blockers (further referred to as "sartans" or "ARBs") are authorised in the EU as a single agent or in combination with other active substances to be administered orally. They are acting on the AT1 receptor subtype thus blocking the effect of angiotensin-II in the renin-angiotensin-system (RAS) cascade.

The concerned ARBs, which are those containing a tetrazole group in their molecular structure authorised in medicinal products in the EU/EEA, are indicated for the treatment of arterial hypertension and for the treatment and prevention of a broad range of cardiovascular diseases. All of these indications concern severe and possibly debilitating diseases. The procedure includes all medicinal products containing candesartan, irbesartan, losartan, olmesartan and valsartan (see figure 1 below).

Figure 1: Angiotensin-II-receptor antagonists/blockers subject to the procedure (tetrazole group circled in red at the example of losartan)



Approved indications include the following areas:

- Candesartan: Hypertension; heart failure in patients with decreased LV function if ACE inhibitors are not tolerated or Add on to ACE inhibitors if mineralocorticoid-receptor-antagonists are not tolerated.
- Irbesartan: Hypertension; treatment of renal disease in adult patients with hypertension and type 2 diabetes as part of the antihypertensive therapy.
- Losartan: Hypertension; treatment of renal disease in adult patients with hypertension and type 2 diabetes as part of the antihypertensive therapy; chronic heart failure; reduction of strokes in adult patients with hypertension and left ventricular hypertrophy.
- Olmesartan: Hypertension.
- Valsartan: Hypertension; treatment of symptomatic heart failure or asymptomatic left ventricular dysfunction after acute myocardial infarction; heart failure.

Indications and/or dose recommendations for the treatment of arterial hypertension in the paediatric population are approved for candesartan, losartan, olmesartan, and valsartan.

Fixed dose combination products containing the above mentioned Angiotensin-II-receptor antagonists are indicated for the treatment of hypertension. All of these ARBs are in wide spread clinical use in the EU.

There are additional ARBs not containing a tetrazole group authorises in the EU, and hence these are not subject to this procedure:

- Azilsartan
- Eprosartan
- Telmisartan

For these ARBs no paediatric indications or dose recommendations have currently been approved.

2.2. Quality aspects

Introduction

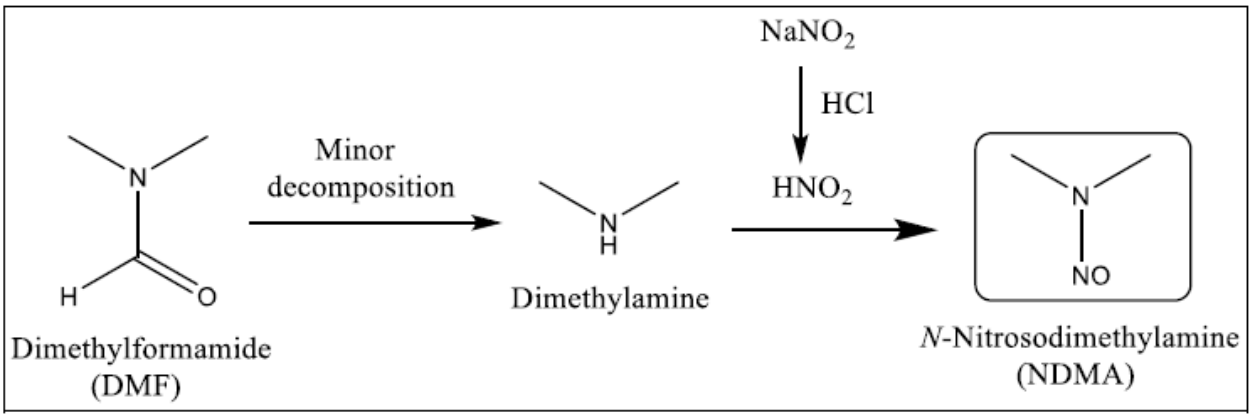
Identification of root causes

In general, the formation of *N*-nitrosamines is only possible in the presence of a secondary or tertiary amine and nitrite, usually under acidic reaction conditions. Additionally, the presence of impurities that can't be formed as part of the process, based on the conditions used, can be explained to an extent by cross-contamination and/or the use of recovered solvents or equipment contaminated with *N*-nitrosamines formed outside of the declared synthetic process.

NDMA

For the formation of NDMA, the presence of the secondary amine dimethylamine (DMA) is important. A possible route to the formation of DMA is the decomposition of dimethylformamide (DMF) at high temperature to DMA (see Fig. 2).

Fig.: 2 Formation of NDMA from DMF

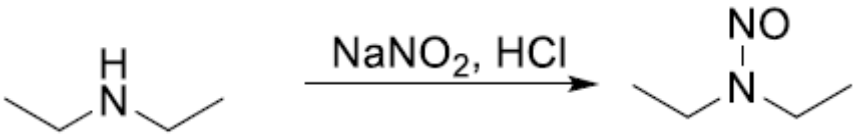


An alternative possibility is that DMA is present as an impurity in DMF since it is a precursor in the industrial DMF synthetic process. It may also be a degradant formed during storage of the solvent, potentially present as the formate salt.

NDEA:

NDEA may be generated from diethylamine (DEA) by analogy to the formation of NDMA from DMA (Fig above).

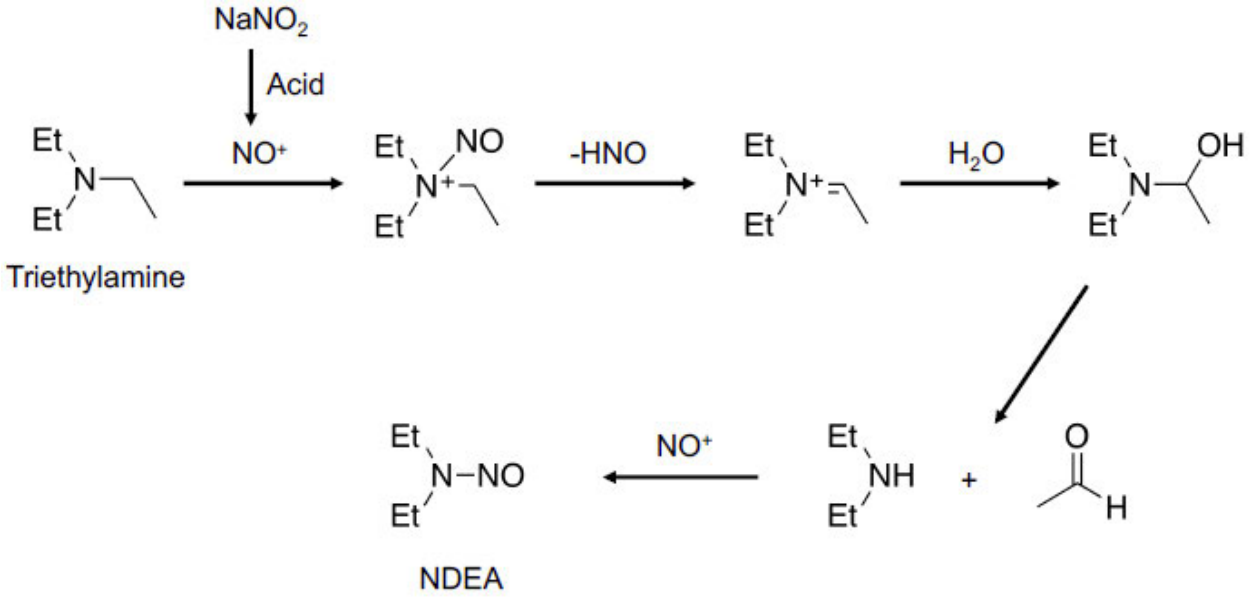
Fig.: 3 General reaction scheme for formation of NDEA from diethylamine



Analogous to DMA formation, DEA could be formed by degradation of triethylamine (TEA) or exist as impurity in TEA raw material.

Alternatively, direct nitrosation of TEA may occur *via* a nitrosoiminium ion, resulting in the generation of an aldehyde and a secondary amine,[1] which reacts with further nitrous acid to form a nitrosamine (Fig. 4).

Fig. 4: Nitrosative cleavage of TEA to DEA followed by nitrosation to NDEA



External sources of contamination:

It is also possible, and has been found during this procedure, that recycled solvents containing NDEA or NDMA are a source of cross-contamination. If solvents used in a reaction step involving azide are recovered and re-used, there is the possibility that *N*-nitrosamines could be inadvertently introduced into the manufacturing process if the waste stream is quenched with nitrite in the presence of secondary or tertiary amines. Solvent recovery is not part of the declared manufacturing process and such risks are therefore not generally assessed by the authorities. Solvent recovery should be carried out according to GMP which requires that recovered solvents meet appropriate standards.

There is a possibility that recycled solvents could be used across manufacturing lines and could result in cross-contamination with *N*-nitrosamines in APIs made by synthetic processes where the synthetic route is not susceptible to the formation of nitrosamines.

There have also been suggestions that process water used in API manufacture could contain low levels of nitrosamines from environmental contamination.

Root cause analysis

Companies whose APIs were contaminated with NDMA or NDEA were requested to provide a thorough root cause analysis during the procedure. Whilst it seems clear that the root cause of the problem is the combination of secondary (or tertiary) amines and $NaNO_2$, usually in the presence of acid, the source of the secondary amine is crucial to any mitigation strategy. Therefore, experimental data or a risk assessment from companies was crucial to determine the source of the secondary amine.

Furthermore, companies were requested to identify additional process parameters which are implicated in *N*-nitrosamine formation (e.g. temperature, stoichiometry, reaction times, work up procedure, etc.).

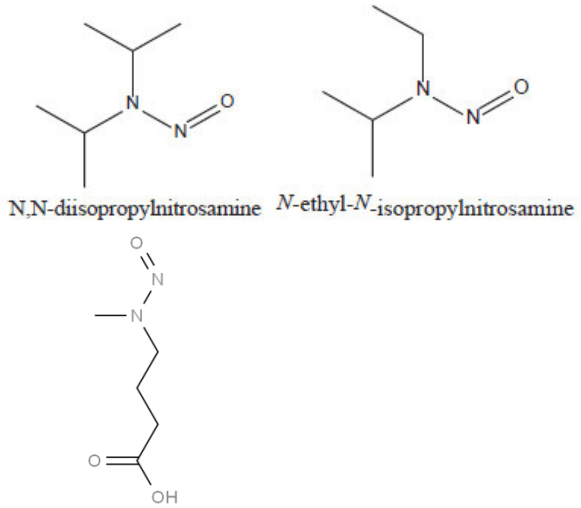
[1] Smith and Loeppky Nitrosative cleavage of tertiary amines J Am Chem Soc 89:5 (March 1 1967)

Several route causes have been proposed as discussed above. However the source of *N*-nitrosamine could be either down to one root cause, or a combination of several, which could also help explain overall variability in contamination. In general, based on the responses received during this referral procedure information on root causes in cases of contamination is still limited.

Other nitrosamines than NDMA or NDEA

Potential contamination with other *N*-nitrosamines was considered during this procedure. Such impurities could be generated if different sources of secondary or tertiary amine are present at the same time as nitrite. Some common organic solvents (e.g. NMP which could give rise to 4-(methyl)(nitroso)amino)butanoic acid = NMBA) and amine bases (e.g. diisopropylamine = DIPEA which could give rise to N-Nitrosodiisopropylamine (DIPNA) and N-Nitrosoethylisopropylamine (EIPNA)) would present such risks. This list of amine-derived solvents and bases is not exhaustive. Therefore, manufacturers and MAHs must take other potential sources of *N*-nitrosamines into account when reviewing their processes and developing appropriate control strategies.

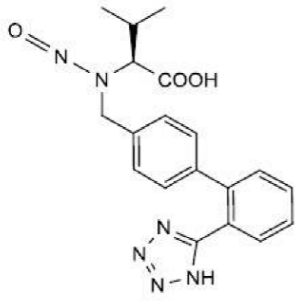
Fig. 5: additional *N*-nitrosamines (DIPNA, EIPNA and NMBA)



4-(methyl)(nitroso)amino)butanoic acid (NMBA)

One API manufacturer reported that a further *N*-nitroso impurity (non mutagenic in Ames test; see also non-clinical section) can be formed in the manufacturing process of valsartan , and it is currently controlled as an "unspecified" impurity at <0.10% (1000 ppm).

Fig. 6: Valsartan *N*-nitroso impurity



EDQM assessment of CEP applications for sartans with a tetrazole ring

Following the detection of *N*-Nitrosamines in valsartan, and subsequently in other sartans with a tetrazole ring EDQM initiated a review of all relevant CEPs in order to identify manufacturing processes at risk of generating *N*-nitrosamines and suspended CEPs as appropriate during their review.

Based on the reviews of responses from API manufacturers and assessments of current CEPs by EDQM in relation to *N*-nitrosamine impurities the CHMP noted that the following CEPs are suspended (as of 31 January 2019):

Valsartan:

- ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD. Xunqiao - Linhai – China; CEP 2010-072
- ZHEJIANG TIANYU PHARMACEUTICAL CO., LTD. CN 318 020 Taizhou –China; CEP 2013-159
- ZHEJIANG CHANGMING PHARMACEUTICAL CO., LTD. Tiantai - Linhai –China; CEP 2014-162
- SIGNA S.A. de C.V. Toluca - Mexico; CEP 2011-231
- AUROBINDO PHARMA LIMITED Hyderabad Telangana -India; CEP 2011-174
- HETERO LABS LIMITED IN 500 018 Hyderabad – India; CEP 2016-069
- MYLAN LABORATORIES LIMITED 500 096 Hyderabad – India; CEP 2009-396

Irbesartan:

- AUROBINDO PHARMA LIMITED Hyderabad Telangana – India; CEP 2009-283
- ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD. Xunqiao - Linhai – China; CEP 2010-033

Losartan potassium:

- ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD. Xunqiao - Linhai – China; CEP 2010-139
- HETERO LABS Hyderabad – India; CEP R1-CEP 2009-247-Rev 02

OMCL Network results

During the procedure, the CHMP liaised with the European network of Official Medicines Control Laboratories (OMCLs) that is coordinated by European Directorate for the Quality of Medicines and Healthcare (EDQM) to conduct a risk-oriented sampling and testing programme of active pharmaceutical ingredients and/or finished products and to inform the European network about any non-compliant results.

The OMCL Network has developed methods for the testing of specific nitrosamines in sartans on the basis of different analytical principles. – The latest information on these methods can be accessed on the EDQM-Homepage (https://www.edqm.eu/en/ad-hoc-projects-omcl-network).

At the time of this report, the Irish OMCL in the Public Analyst's Laboratory in Galway (PALG), the French OMCL at the ANSM site in Montpellier and the Chemisches und Veterinär-Untersuchungsamt (CVUA) Karlsruhe as well as the LGL Bayern established analytical methods for quantification of NDMA and NDEA on behalf of the Network. Additionally, the U.S. FDA, the Taiwan FDA, Health Canada and Swissmedic have published methods for the simultaneous determination of NDMA and NDEA[2].

In view of the results from OMCLs, the CHMP noted that comparisons of valsartan API and related finished products (FP) indicate that in the majority of the cases, FP contain a lower amount of NDMA than in corresponding API batches, although in some cases, the amount was higher in the finished

[2] U.S. FDA: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM623198.pdf
https://www.fda.gov/downloads/Drugs/DrugSafety/UCM623578.pdf

Taiwan FDA: https://www.fda.gov.tw/tc/includes/GetFile.ashx?mid=189&id=27626

Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/angiotensin-receptor-blocker.html

Swissmedic: https://www.edqm.eu/en/ad-hoc-projects-omcl-network
https://www.swissmedic.ch/swissmedic/en/home/news/mitteilungen/ndma-ndea-in-sartans-test-method.html

product (range +10 to -51%). This variability could be explained by a loss of NDMA during formulation, non-homogeneous distribution of the impurity, or variability in sampling and analysis.

In view of co-contamination with both NDMA and NDEA so far in 22 valsartan API batches manufactured by ZH NDMA and NDEA have been detected. Mostly, NDEA was low when NDMA was high and vice versa. Only in three batches NDEA and NDMA where present in similar amounts between 4.4 and 10 ppm (see table 1 below).

Table 1: Example of 3 API batches of valsartan from ZH with similar NDMA and NDEA levels

Batch	NDMA (ppm)	NDEA (ppm)
1	10,0	9,15
2	9,2	8,05
3	4,4	4,74

Data from MAHs and API manufacturers

Candesartan

In the responses received from MAHs or API manufacturers of candesartan, no levels of the NDMA and NDEA impurities above the acceptable intake (AI) levels, i.e. daily intake levels calculated based on ICH M7(R1) (see non-clinical section below), have been noted. The level of information is variable, where some MAHs give a clear description of the syntheses used, the risk assessments as adopted by the MAH and information on batch analyses and information on the method validation. However, many MAHs did not provide their own risk assessment but included information from the FP manufacturer and/or API manufacturer.

More than half of MAHs have confirmed that the synthesis route includes steps that may potentially lead to the generation of *N*-nitrosamines.

Generally, none of the batch analyses that have been reported by companies during the procedure showed levels of NDMA or NDEA above the thresholds (all not detected, although the limit of detection (LoD) differs between methods used). All results come from analyses of the drug substance, apart from one batch analysis on finished product. Whilst, many of the methods used for analysis were not fully validated, results can be seen as an indication that these impurities are not likely to carry over to the drug substance. This is in line with the knowledge that the tetrazole ring-forming step of the synthesis of candesartan often is introduced early in the synthesis, thus giving opportunity for removal of NDMA and NDEA in subsequent purification steps.

Irbesartan

In the responses received from API manufacturers and MAHs, relevant differences are observed regarding the information provided. Some of them submitted the complete route of synthesis and others only provided a statement confirming the absence of *N*-nitroso impurities.

Most of the API manufacturers declare that *N*-nitroso impurities are not potentially present in the final API since the values found are below the safety limit or even not detected. However, taking into account the routes of synthesis, NDEA is a potential impurity in many of them and the presented limited data does not preclude the need to establish an adequate control strategy.

None of the API manufacturers has made reference to the possible presence of these impurities in the final API due to the use of recovered solvents.

API sourced from Aurobindo Pharma Ltd. is the only API with NDEA levels found to be higher than the AI levels calculated based on ICH M7(R1) (see non-clinical section below). The API manufacturer has provided a detailed discussion about the unlikely formation of *N*-nitrosamine impurities for an optimized process and results on the content of NDEA and NDMA in API, intermediate and starting materials. The suitability of this optimized process is currently being assessed by EDQM.

No analytical data of *N*-nitroso impurities from finished product batches has been submitted.

Losartan

Although batch analysis data submitted by MAHs and API manufacturers showed that NDMA or NDEA has not been detected in losartan drug substance batches above the limits based on ICH M7 (R1) (see non-clinical section below), contamination of Losartan is generally possible. The CHMP noted that two losartan CEPs have been suspended (see above) based on the EDQM's CEP assessment, and OMCL testing found NDEA in finished product samples close to the above limits.

In addition, 4-(methyl)(nitroso)amino)butanoic acid (BMSA/NMBA) has been reported during the procedure as a potential impurity in losartan from one MAH and actually detected in losartan batches of Hetero Labs (see non-clinical section below on toxicology aspects). NMBA could be formed during the synthesis of losartan while using sodium nitrite and *N*-methylpyrrolidone.

Olmesartan

In general, only theoretical discussion of the potential formation of *N*-nitroso-compounds (mainly NDMA and NDEA) has been performed by several MAHs and API manufacturers.

In about 50% of the responses, the assumption that NDMA and NDEA cannot be formed is supported by batch data (API testing only). In some cases, method validation data are missing. Additional validation data for GC-MS determination of NDMA and NDEA in API have however been provided late by one API manufacturer.

Batch results from API testing are in-line with the OMCL API/finished product testing (NDMA and NDEA have not been found in olmesartan API/FP so far).

Valsartan

Answers received from API Manufacturers and MAHs in general do not allow definite conclusions.

In order to achieve a reliable comparison of analytical data on *N*-nitrosamines detection, API manufacturers and MAHs were asked to preferably use one of the three analytical methods used by OMCLs and published on 21 September 2018 (https://www.edqm.eu/en/news/omcls-release-three-methods-determination-ndma-sartans).

-The PALG method is based on Headspace-GC-MS (single quad) and applicable to the determination of NDMA in API and corresponding FPs of the sartan group.

-The ANSM method uses HPLC-UV as general analytical principle for the determination of NDMA in valsartan (API and FP).

-The CVUA Karlsruhe method is based on APCI-UHPLC-MS/MS and applicable to the detection and quantitative determination of NDMA in valsartan finished products.

In view of analytical data, out of 34 MAHs who answered, 11 MAHs provided analytical data on the content of NDMA in their FPs and 5 MAHs in API used in their FPs.

All MAHs but one were able to provide data on NDEA amount in finished product and the corresponding API, while two other MAHs provided data on NDEA in API only. The limited number of data on NDEA in valsartan was due to the unavailability of validated analytical methods.

The highest mean value of NDMA found in finished products (using API by ZH) was 75.4 ppm; this was used to calculate the excess risk. The highest mean value of NDMA was found by an MAH in ZH API (61.3 ppm).

Four MAHs tested the presence of NDMA in both API and corresponding FPs. Unfortunately, the lack of a robust correlation (potential carry-over – see below) hampers the possibility to perform a sound risk assessment.

Four out of 14 valsartan API manufacturers which answered to the LoQs, provided analytical data on the content of NDMA in their APIs; the highest mean value was found by ZH; being 60.13 ppm.

Two API manufacturers also provided analytical data on NDEA. The highest mean value was 11.53 ppm – this was used to calculate the excess risk.

Some API manufacturers only declared that the process does not involve the use of sodium nitrite, claiming that the process could not lead to formation of NDMA & NDEA in drug substance. This statement was only in few cases supported by batch analysis results on *N*-nitrosamine content confirming these claims, in an adequate number of batches.

Some others provided a flowchart of the manufacturing process starting from an advanced intermediate. In general, only limited information has been provided by the API manufacturers to fully assess possible contamination. A detailed description of the relevant process steps including quenching of sodium azide, work-up, phase separation and extraction procedures as well as information on waste streams would be needed to rule out possible *N*-nitrosamines formation. Any further possible contamination coming from raw materials should be investigated, e.g. recycled solvents or reagents, possible contamination of NDMA and NDEA in the water or possible presence of nitrite in sodium azide. The CHMP also noted that information on adequate purge of azide (which is itself highly reactive and a human mutagen) and batch data demonstrating its absence in the API or specification limits have not been consistently presented as part of the responses. The CHMP recommends that MAHs should take the above into account when reviewing the manufacturing process.

It is noted that only some API manufacturers discussed the possible formation and mutagenicity of other *N*-nitrosamines, further than NDMA and NDEA.

Potential carry-over of impurities from API to finished product has been studied considering MAH results as well as OMCL findings. Different trends were observed, with most of the analyses showing lower NDMA amounts in the finished product batch than in the corresponding API batch and some showing higher amounts in the finished product batch compared with the corresponding API batch.

Co-presence of NDMA and NDEA above the lowest LoD (0.025 ppm for NDEA) was observed in 22 out of 119 valsartan API batches produced by ZH from 2012 to 2016 using the "new" $ZnCl_2$ process. In the majority (n. 15) of the compared batches, NDMA was higher than NDEA. In the batch where NDMA was highest (59 ppm), NDEA was very low (0.71 ppm); in the batch where NDEA was highest (30.76 ppm), NDMA was very low (0.22 ppm). Only in three valsartan ZH API batches the ratio between NDEA and NDMA was approx 1:1 (10.0ppm NDMA and 9.15ppm NDEA; 9.2ppm NDMA and 8.05ppm NDEA and 4.4ppm NDMA and 4.74ppm NDEA).

Additional *N*-nitrosamines

DIPNA and EIPNA

In a previously used synthetic route of one manufacturer, *N*,*N*-diisopropylethyl-N-ethylamine (DIPEA) was used as a base for intermediate compounds in the manufacturing process for valsartan. This synthetic route is not in-use anymore since 2014. The use of DIPEA could potentially lead to the formation of two *N*-nitrosamines namely *N*-nitrosodiisopropylamine (DIPNA) or *N*-nitrosoethylisopropylamine (EIPNA).

Six valsartan API batches from 2015 (retained samples) have been tested by the manufacturer, in which DIPNA and EIPNA were < 0.1 ppm; analytical test of DIPNA and EIPNA in valsartan FPs are not available yet.

Another valsartan manufacturer is also using DIPEA in its manufacturing process. Although the manufacturer states that the possibility of *N*-Nitroso compounds i.e. *N*-Nitroso-diisopropylamine (DIPNA or NDIPA or NDIA) and *N*-Nitroso-isopropylethylamine (EIPNA or NEIPA or NEIA) is unlikely in the manufacturing process followed for an intermediate, it is noted that DIPEA is used for the manufacturing of this intermediate. Therefore, the formation of DIPNA and EIPNA cannot be ruled out.

Ten valsartan API batches from a manufacturer have been tested with a validated GC-MS for the simultaneous detection of NDMA, NDEA, NDIPA and NIPEA. LoQ and LoD are set at 0.03 ppm and 0.01 ppm, respectively for all the four impurities. In all tested valsartan batches, the content of the four impurities was below 0.01 ppm.

Discussion and conclusion on quality aspects

The CHMP considered all the available information and despite limitations of the information e.g. on many manufacturing processes, validation of analytical methods, etc., it is unlikely that further relevant information could be expected that would alter the risk assessment and the overall recommendation for controlling *N*-Nitrosamine contaminations prospectively.

From the root cause analysis, several sources for contamination with *N*-nitrosamines were identified:

- formation of *N*-nitrosamines due to the simultaneous presence of a secondary or tertiary amine and nitrite, usually under acidic reaction conditions
- cross-contamination
- use of recovered and contaminated solvents, reagents or equipment

Therefore and having considered all available data and the Quality Working Party's (QWPs) conclusions, the CHMP recommends that the following measures should be taken into account, as appropriate, for minimising the risk of all *N*-nitrosamine contamination:

- As main priority, use reaction conditions where the possibility of *N*-nitrosamine contamination is avoided. This could involve using different solvents (i.e. not amides such as DMF, DMA, NMP), different bases without secondary/tertiary amines (e.g. inorganic bases), or more hindered and thus less reactive amine bases.
- Change the order of reactions, introducing the tetrazole moiety at an earlier step – this gives more opportunity for purge of *N*-nitrosamines through subsequent synthesis steps and purification operations. Steps involving mutagens should be carried out as early as possible in the synthetic sequence.

- Off-line quenching of azide, following separation of aqueous and organic layers. The repartition of azide between aqueous and organic phases and the residual quantities following washing in the product layer needs to be characterised;
- Replacement of $NaNO_2$ with alternative quenching agents (for azide destruction);
- The use of recovered solvents from steps where there is a risk of *N*-nitrosamine formation (either as part of the API process or as part of the recovery process) should be avoided, or it should be demonstrated that *N*-nitrosamines are adequately purged (i.e. they should be limited by specification). This applies particularly to the final step;
- Control of raw materials that may introduce nitrite (NO_2^-) or *N*-nitrosamines, e.g. sodium azide, solvents and water;

Overall, it is concluded that *N*-nitrosamines in finished products can be effectively controlled by using a synthesis pathway minimising as much as possible formation of these impurities and observing GMP requirements (cleaning of equipment; control of recovery process for solvents, etc.).

In terms of carryover of *N*-nitrosamine impurities from active substance to finished product, a 1:1 correlation could be assumed as “worst case” scenario for both NDMA and NDEA since there are no reasons to expect an increase in *N*-nitrosamine impurities from API to finished product.

The CHMP considers that the use of AI limits calculated based on ICH M7(R1) (see non-clinical section below) are acceptable as specification limits of API for a transitional period (of two years) during which risk assessments and, if necessary, changes in manufacturing processes should be performed to minimise as much as possible *N*-nitrosamines presence and to avoid drug shortages.

After that, limits for NDMA and NDEA lower than the AI levels and defined based on technical feasibility of analytical methods should be in place. Preferably, a reference method should be developed and validated by cooperative inter-laboratory testing and comparison of results. This procedure should be coordinated by EDQM and the results finally published in the European Pharmacopoeia. After the transition period, manufacturers will need to show nitrosamine levels in their API to be non-quantifiable in a sensitive and validated assay. A specification limit should be set based on technical capability, which should preferably be derived from the LoQ of a suitably sensitive analytical method, which is also in line with the QWP feedback (see below). The underlying concept is that – for long-term exposure - NDMA and NDEA levels should be as low as possible in any sartan API without regard to type of sartan or dose. A limit of 0.03 ppm appears achievable according to the data from the OMCL network (see OMCL section above). Therefore, the transition period should also be used by manufacturers to adapt their analytical methods such that they are sensitive enough to measure levels commensurate with the future API specifications for NDMA and NDEA.

When comparing data on API and finished product provided by OMCLs and MAHs, NDMA concentrations – although largely fluctuating - were in generally lower in finished product batches compared to corresponding API batches. No conclusion is possible regarding the potential carry-over for NDEA due to the limited data provided.

Overall, a 1:1 correlation could be assumed as “worst case” scenario for both NDMA and NDEA since there are no reasons to expect an increase of process impurities from API to finished product.

In view of co-presence of NDMA and NDEA, as reported by ZH, mostly, NDEA was low when NDMA was high and vice versa. Only in three batches NDEA and NDMA where present in similar amounts between 4.4 and 10 ppm.

In addition, the CHMP considers that the formation of valsartan *N*-nitrosamine impurity (Fig.4) further demonstrates that if a secondary amine is present and a combination of $NaNO_2$/acid are used, then *N*-nitrosamines will generally be formed.

As concerns the control strategy, only a few MAHs propose to include NDMA/NDEA specification and analytical testing for finished medicinal products. Most of the MAHs propose that the NDMA/NDEA control should be included at the level of the API itself.

Overall considerations

In view of analytical aspects, the available methods differ in their LoD and LoQ, however currently, a LoQ of 0.03 ppm for NDMA and NDEA would be achievable according to the data from the OMCL network (as outlined in the OMCL section above). QWP also supported that any technical limit should be based on the LoQ, which would be used to derive a threshold (see section on expert consultation below). In comparison to the AI levels calculated based on ICH M7(R1) (see section 2.3 non-clinical aspects below for details), it is possible to generate additional safety factors ranging from 2.73 – 27.3 for NDMA and 10.0 – 100 for NDEA, respectively, by defining 0.03 ppm as the common technical target limit for NDEA and NDMA in tetrazole sartan APIs (see table 2 below).

Table 2 Comparison of calculated ppm/day for each sartan and technical target limit of not more than 0.03 ppm

Drug substance*	Max. daily dose (mg)	NDEA Acceptable Intake (ng/day)	NDEA Acceptable Intake (ppm/day in API)	NDEA Technical target limit (ppm/day in API)	NDEA Additional Safety factor
Valsartan	320	26.5	0.082	0.03	2.73
Losartan	150	26.5	0.177	0.03	5.90
Olmesartan	40	26.5	0.663	0.03	22.1
Irbesartan	300	26.5	0.088	0.03	2.93
Candesartan	32	26.5	0.820	0.03	27.3
Drug substance*	**Max. daily dose (mg)**	**NDMA Acceptable Intake (ng/day)**	**NDMA Acceptable intake (ppm/day in API)**	**NDMA Technical target limit (ppm/day in API)**	**NDMA Additional Safety factor**
Valsartan	320	96.0	0.300	0.03	10.0
Losartan	150	96.0	0.640	0.03	21.3
Olmesartan	40	96.0	2.400	0.03	80.0
Irbesartan	300	96.0	0.320	0.03	10.7
Candesartan	32	96.0	3.000	0.03	100

The underlying concept of the proposed approach is to keep NDMA and NDEA contaminations as low as technically possible, without regard to type of sartan or dose.

The approach to control the nitrosamines at API level proposed by some MAHs is endorsed considering that they are process impurities. The approach to control the impurities both by acting on the synthetic process to reduce/remove the impurities as much as possible and by in the meantime setting adequate specifications at API level, is also endorsed. The above considerations for root causes should be taken into consideration when reviewing the manufacturing process in order to reach the final target of 0.03 ppm for NDMA and NDEA.

Based on the considerations above, the risk of *N*-Nitrosamine contamination is in principle possible across the class of sartans with a tetrazole ring, and thus, measures to control contamination risk should be applicable for all of the corresponding products.

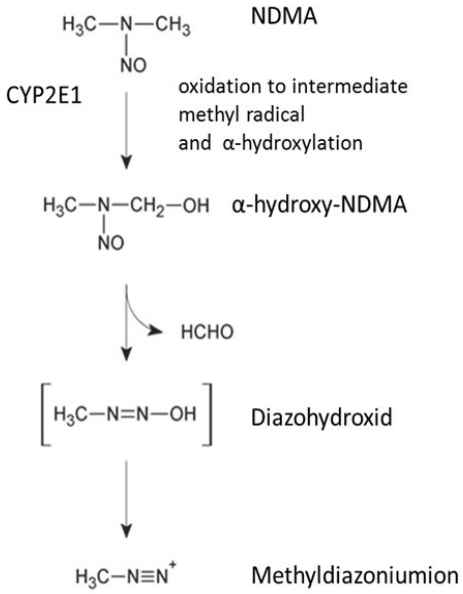
2.3. Non-clinical aspects

Introduction

NDMA and NDEA Toxicology

NDMA is metabolized primarily by CYP2E1 in liver of rodents finally leading to the generation of a methyldiazonium ion (Sulc et al., 2010) (Fig. 7) which can react with DNA and predominantly forms N^7 and O^6-methylguanine (N^7MG and O^6MG), the latter being highly mutagenic. Error-free repair of O^6MG is done by O^6-Methylguanin-DNA-Methyltransferase (MGMT), a suicide enzyme with limited capacity in cells. O^6MG and to a lesser extend N^7MG are relevant mutagenic lesions which have been shown to increase in animals following NDMA exposure.

Fig. 7: Metabolic activation of NDMA formation of the DNA-reactive methyldiazoniumion from NDMA (adapted from Sulc et al., 2010)



NDEA is metabolized in humans primarily by CYP2E1 and CYP2A6. The metabolism is considered similar to NDMA with the primary activation step by α-hydroxylation to α-hydroxyl-NDEA and finally leading to an ethyldiazonium ion reacting with DNA and formation of O^4-ethyldeoxythymidine (O^4ET) and O^6 ethylguanin (O^6EG) as the primary mutagenic adducts (Verna et al. 1996). In liver of male fisher rats O^6EG and O^4ET increased dose dependently with NDEA reaching maximum after 6 h. Whereas O^6MG diminished after 24h, O^4ET and the minor adduct O^2ET were persistent even after 20 days. This may be due to the difference in repair mechanism. While alkyltransferase (AT) effectively repairs O^6EG, O^4ET repair seems to be much slower and less effective (Pegg et al. 1984, Dragan et al. 1994).

NDMA and NDEA cause increases in mutations in different organs in mouse (Jiao et al., 1997, Chen et al. 1993) and NDMA and NDEA cause cancer in various species and different organs of laboratory

animals with liver being a primary target organ in all species (The Carcinogenic Potency Database, CPDB - online). The carcinogenicity studies in rats from Peto et al., (1991) are considered the most extensive and most relevant studies to be used for human risk assessment.

With regards to human data, there are publications on acute toxicity and on endogenous formation of NDMA and NDEA (Hu et al 2016). Some epidemiological studies have used estimations of exogenous NDMA exposure and in one case also NDEA exposure derived from food intake questionnaires. These have suggested an association between exposure and development of cancer (mainly stomach, rectal and pancreatic cancer) in humans (Knekt et al., 1999, Loh et al., 2011, Song et al. 2015, Zheng et al, 2018). The weakness of such studies however is that only the NDMA content was estimated whereas the contents of other carcinogens that may be present in food, like polycyclic aromatic hydrocarbons (PAHs), were not. PAHs and other carcinogens are usually present in higher concentrations than volatile *N*-nitrosamines. Therefore, interpretation of these studies remains questionable.

As happening in a real life context, intake of NDMA and NDEA should be seen in relation to the overall intake of carcinogens, e.g. as benzo[*a*]pyrene and other PAHs and also other nitrosamines that are present in common food sources, such as grilled meat. Exogenous intake of NDMA and NDEA is however considered to be lower than intake of some other carcinogens. The amount of NDMA and NDEA coming from endogenous sources through conversion of amines to NDMA and NDEA in gastric and other acid tissue environments is described to be higher than general exogenous exposure (Krul et al. 2004; Zeilmaker et al., 2010; Zeng and Mitch, 2016, Hu et al. 2016). In this respect, endogenous NDMA and NDEA generation can depend on specific patient characteristics, e.g. higher NDMA and NDEA levels were observed in patients with inflammatory conditions or infections than in healthy individuals. Limited data in patients also show that endogenous NDMA and NDEA exposure increases with ethanol consumption (Dunn et al., 1990; Verna et al. 1996, Hu et al., 2016; Dunn, 1989). The potential impact of patient characteristics, such as metabolic enzyme activity of CYP2E1, CYP2A6 (Wang et al., 2003), but also CYP3A6 and CYP2B4 (metabolic conversion of this nitrosamine to highly reactive species), individual repair capacity of O^6MG and O^6EG via O^6-alkylguanine DNA alkyltransferase (Margison et al., 2003), and health status may affect the individual subject's risk. However, it is acknowledged that these data may not be available for patients. There is strong evidence that the toxicological effects of NDMA and NDEA depend on metabolic activation by CYP2E1 and/or CYP2A6 and DNA-repair capacities for the specific DNA-adducts formed, e.g. MGMT-dependent repair capacity (Smith et al., 1998; Anderson et al., 1996; Hall et al., 1985).

Detection of NDMA/NDEA in APIs / finished products

NDMA and NDEA above the AI levels defined based on the principles of ICH M7(R1) have been found retrospectively in valsartan batches manufactured by ZH. NDMA or NDEA above the AI level were also found e.g. in valsartan batches manufactured by ZT and Mylan, losartan batches manufactured by Hetero Labs and in irbesartan batches manufactured by Aurobindo. For risk assessment, it currently seems prudent to perform excess risk calculations using the highest mean amounts found in finished products and the levels reported to be found in APIs.

Exposure to NDMA in contaminated sartan tablets and API batches

NDMA concentrations in valsartan API batches have been measured retrospectively by the API manufacturers, MAHs and by OMCLs of the EDQM network. Published results are also available for a few finished product samples taken from pharmacies by Zentrallaboratorium Deutscher Apotheker e.V. (DAZ – online 2018).

The highest number of API batches measured with highest impurity values was manufactured from ZH. Therefore, it is not surprising that the tablets with highest measured values of NDMA were manufactured using ZH API. To be cautious and using a conservative approach for risk assessment, the

mean values of the API batches manufactured by ZH are used and also the highest mean of NDMA found in the finished products of the MAHs which provided data. The highest mean levels of NDMA were found in a finished product using ZH API.

The highest NDMA mean values found, which are used for further excess risk calculations are summarized in the table below:

Table 3 Highest NDMA mean values found in API and FP

Source	Number of batch/samples	NDMA ppm (µg/g)		
		Mean	Highest	Lowest
Valsartan API by ZH	6833	**60.13**	**240.1**	0.1
Valsartan FP containing API by ZH)	5	**75.4**	**97.4**	56.7

It is assumed that the amount of NDMA in the drug substance batches is fully (1:1) transferred into the respective finished product as outlined in the Quality section above.

It seems therefore reasonable to continue performing further calculations of excess risk using the data of the API batches submitted by ZH and the above data from finished product using ZH API and assuming a 1:1 transfer of NDMA from API into finished product.

Therefore, the situation which CHMP considers as a realistic worst case exposure is highlighted by the following main points:

- maximum duration of exposure of patients to NDMA contaminated valsartan of 6 years (since July 2012 to July 2018).
- 240.1 ppm as the highest NDMA contamination found in ZH API batches, as communicated by ZH. This would result in 76.8 µg/day in a 320 mg valsartan tablet.
- 60.13 ppm as the mean NDMA contamination found in ZH API batches. This would result in 19.24 µg/day in a 320 mg valsartan tablet.
- 75.4 ppm as the highest mean NDMA contamination found by one MAH in valsartan tablets manufactured using ZH API, corresponding to 24.1 µg/day in a 320 mg valsartan tablet. 24.1 µg is used as the maximum average daily exposure of patients in further excess risk calculations. This value is the highest mean measured in tablets so far and still close to the average measured in ZH API batches.

The average daily exposure to NDMA due to contaminated beverages and food, air and water pollution is assumed as within an order of magnitude 100 – 1,000 ng/day = 0.1 – 1 µg/day (Keszei et al. 2013; N-NITROSODIMETHYLAMINE. WHO. Geneva, 2002). Thus, NDMA exposure associated with contaminated valsartan tablets (containing API from ZH) containing the mean NDMA levels is approximately 24 to 240 times higher than the daily exposure through beverages and food, air and water pollution.

Exposure to NDEA in contaminated sartan tablets and API batches

NDEA concentrations in valsartan API batches have also been measured retrospectively by the API manufacturer ZH and by OMCLs of the EDQM network in some API batches and FP. More than two months after finding NDMA in API batches of valsartan, ZH informed customers and the authorities of having also found NDEA in older batches of valsartan manufactured between 2011 and 2015. ZH provided analyses results for NDEA of 201 valsartan batches. Analyses results from finished products

for NDEA contamination are very limited. Only two MAHs provided some data for NDEA in finished products as well as API. One of the MAHs used ZH APIs. Swissmedic measured NDEA in API and finished product from Mylan at levels >0.083 ppm. Mylan submitted results for 42 API batches (see table below); 17 were reported to also contain NDMA below 0.3 ppm. Aurobindo submitted data for 79 batches irbesartan finished product and 94 batches Irbesartan API. Heterolabs found NDEA in 25 of 535 losartan batches analysed. Only four were above 0.083 ppm with a maximum of 0.15 ppm. The few data available suggest considerable lower NDEA values in finished products compared to corresponding API batches. However, there are also few cases with higher NDEA levels in finished product than in the API it was made of.

Table 4: NDEA concentrations found in sartan API and FP

Source	Number of batch/samples	NDEA ppm (µg/g)		
		Mean	Highest	Lowest
Valsartan API by ZH	201	**11.53**	**42.14**	0.03
Valsartan API by Mylan	42	**0.35**	**0.74**	0.08
Valsartan FP by Zaklady vanatex	4	**1.32**	**1.32**	<LoD
Losartan API by Hetero Labs	535	**0.75**	**0.15**	<LoD
Irbesartan API by Aurobindo	94		**0.64**	<0.01
Irbesartan FP by Aurobindo	79	**0.104**	**0.215**	<LoD

Due to limited data of finished products no conclusions on the transfer rate from API to finished product can be drawn.

For calculations of potential excess cancer risk of NDEA exposure, the mean API contamination levels found in ZH API batches with 11.53 ppm equivalent to 3.7 µg/d for 320 mg valsartan tablets is used to provide a conservative worst case estimate. For duration of potential exposure 4 years, are assumed to be a conservative estimate based on the duration of manufacture of potentially contaminated batches by ZH from 2011 - 2015.

In Irbesartan API of Aurobindo only low levels of NDEA were found in batches manufactured 2016 – 2018. Considering the low levels and the limited potential exposure period, no excess risk above 1 additional cancer case among 100,000 subjects exposed a life time is estimated.

Co-Exposure to NDMA and NDEA

As outlined in the section on quality above, mostly, NDEA was low when NDMA was high and vice versa. Only in three API batches NDEA and NDMA where present in similar amounts between 4.4 and 10 ppm.

Data on co-contamination are very limited. The worst case scenario for excess risk calculations is therefore still assumed to be batches finished product manufactured using ZH API containing mean

values of 75.4 ppm NDMA (24.1 µg in 320 mg valsartan) and of ZH API with 11.53 ppm NDEA (3.7 µg).

Compound acceptable intake (AI) levels

NDMA is a potent mutagenic carcinogen in a number of different animal species. On the basis of animal data (rat being the most sensitive species), NDMA is classified by the IARC as “probably carcinogenic to humans” (Class 2A carcinogen). This classification is used by IARC when there is "limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals". Other long-term effects, such as severe hepatotoxicity have also been observed in rhesus monkeys with this class of nitrosamines.

Although NDMA itself does no react with DNA and metabolic activation is needed to form the DNA-reactive molecule as outlined above, in risk assessment NDMA is however regarded as a DNA reactive carcinogen. For such compounds any exposure level is considered to pose a risk and safe level without a risk cannot be established. Although this general paradigm is currently challenged, the scientific debate has not come to an acceptable conclusion yet. An increased theoretical lifetime cancer risk of 1 additional case in 100,000 treated patients i.e. increased lifetime cancer risk of 1:100,000, is the generally accepted risk level for impurities in pharmaceutical products (ICH M7(R1)).

NDMA belongs to *N*-nitroso compounds, which are part of the so-called “cohort of concern” described in the ICH guideline M7(R1). For such compounds the generic TTC of 1.5 µg/day as an AI for mutagenic impurities is not considered applicable and a compound specific AI needs to be derived from compound specific carcinogenicity data.

The generally accepted approach recommended by ICH M7(R1) is to use either the dose giving a 50% tumour incidence (TD_{50}) or the Bench Mark Dose Lower Bound Confidence Limit ($BMDL_{10}$), an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents, as the point of departure for the calculation of excess cancer risk.

A well acknowledged and accepted source for TD_{50} values from cancer studies is the Carcinogenic Potency Database (CPDB; online).

The TD_{50} listed there for NDMA is 0.096 mg/kg/day (in the most sensitive species, the rat) calculated as harmonic mean from all positive studies in rats including the data of the Peto et al. 1991 study. The extrapolation to the excess risk level for cancer is performed by linear back extrapolation to the dose theoretically causing a 1:100,000 risk by dividing the TD_{50} by 50,000 (50% or 0.5 x 100,000). For NDMA this translates into a dose of 1.92 ng/kg/day. For a person with a bodyweight of 50 kg this would result in an AI level of **96 ng/day** (50 x 1.92 ng). 96 ng/day correspond to **0.3 ppm** in a 320 mg valsartan tablet.

Table 5: NDMA amounts associated to a 1:100,000 excess risk in ng and ppm for maximum daily doses of sartans

API	max daily dose mg	NDMA acceptable intake (AI) level (ng)	NDMA ppm
Valsartan	320	96.0	0.300
Losartan	150	96.0	0.640
Olmesartan	40	96.0	2.400
Irbesartan	300	96.0	0.320
Candesartan	32	96.0	3.000

According to the Haber's rule, a fundamental principle in toxicology generally accepted to be used for mutagenic carcinogens and therefore considered appropriate for NDMA, the total dose taken over time (dose x time) produces a fixed level of effect, thus, determining the risk associated with the exposure. Applying this very conservative principle, the cumulated dose acceptable for lifetime is then the AI multiplied by the days of a lifetime (70 years is generally accepted for this) of 25,550 days. Using the AI calculated from TD_{50} i.e. 96 ng/day results in a lifetime acceptable dose associated with a 1:100,000 additional cancer risk of 2453 µg.

As the maximum duration of exposure to NDMA from contaminated valsartan is 6 years or 2190 days the AI for 6 years can be calculated by dividing by 2190 resulting in: 1.12 µg/day as AI over 6 years. Doubling of this intake doubles the risk from 1:100,000 to 1:50,000 and so on.

The approach based on TD_{50} was first used to determine regulatory action levels (to set an action limit for NDMA in new valsartan API) and first excess cancer risk calculations for the realistic worst-case exposure scenario as outlined above. This calculations resulted in a theoretical excess lifetime cancer risk of 1:5000 (0.02%) for taking daily 320 mg valsartan contaminated with 24.1 µg NDMA (the highest amount tested in valsartan FP).

NDEA, like NDMA, is also classified by IARC as "probably carcinogenic to humans".

Several TD_{50} values for NDEA are listed in the CPDB for rat, cynomolgus monkey and bush babies. The lowest calculated TD_{50} is 0.00725 mg/kg/day for liver tumours in the cynomolgus monkey. The TD_{50} for NDEA obtained in the rat is 0.0265 mg/kg/day. In rat besides liver tumours also other tumours were reported e.g. oesophagus, kidney, and vasculature in male rat.

The extrapolation to the excess risk level for cancer is then done the same way as for NDMA by linear back extrapolation to the dose theoretically causing a 1:100,000 risk by dividing the TD_{50} by 50.000 (50% or 0.5 x 100,000). For NDEA this translates into a dose of 0.144 ng/kg/day extrapolated from cynomolgus monkeys and 0.53 ng/kg/day extrapolated from rat. For a person with a bodyweight of 50 kg this would result in an AI level of 7.2 ng/day (50 x 0.144 ng) or 26.5 ng/day (50 x 0.53 ng). 7.2 ng is equal to **0.0225 ppm** and 26.5 ng is equal to **0.083 ppm** in a 320 mg valsartan tablet.

The difference between TD_{50} values based on different studies/calculations is considered significant. For the NDEA risk assessment it is therefore considered necessary to first assess the most appropriate TD_{50} to be used as a starting point.

As outlined above there are at least two different models to calculate excess cancer risk from animal studies. Both rely on mathematical models to first fit experimental animal data to calculate a virtual continuous dose response curve and set benchmarks (e.g. TD_{50} and $BMDL_{10}$) which are then used to extrapolate into a never tested extremely low dose range and calculate theoretical risk levels (e.g. 1 in 100,000 additional cancer risk) for ultralow doses. It seems clear that variability of doses calculated in this way may be significant depending on the quality of animal experiments, number of doses tested in the experiment, group size of dose groups in animal tests and extrapolation models.

The critical evaluation of the animal species data (rat or cynomolgus monkey) to use for the NDEA excess risk calculation highlights the strength and limitations of the rat and monkey datasets. Although it cannot be excluded that the non-human primates may be a more relevant model, the huge dataset for rat with 14 studies with up to 15 doses tested would provide a much more robust and accurate calculation of the dose response curve. Furthermore, the monkeys were dosed i.p. whereas the rat were dosed orally. In the most sensitive study in cynomolgus monkeys a huge interval of more than 300 µg/day was chosen between the lowest dose and the second dose. The second dose already caused cancer in all of the only 3 animals in that group. The group size of all intermediate dosage groups was small with only 3 to 7 animals per group. The most extensive rat study used 9 ascending

doses in the same dose range and 60 animals per group. Only 2 studies in cynomolgus monkeys are available with the second study only using one dose compared to 8 studies in total for the rat (5 with more than one dose group). A summary of the study outlines is given below. It was therefore concluded that the TD_{50} calculated for the cynomolgus monkey studies is most likely more unreliable compared to the TD_{50} calculated for the rat studies.

Table 6 Summary of animal studies with NDEA used to calculate harmonized means for TD_{50}

Species	Studies	Max number of doses	Dose range covered mg/kg/day	Maximum duration
Bush baby	1	1	0, 0.897	32 m
Cynomolgus monkey	2	5	0, 0.0063, 0.322, 0,91, 1.35, 2.29, 8.07	16 y
Rhesus monkey	2	6	0, 0.0074, 0.08, 0.34, 0.65, 1.59, 2.09, 6.87	22 y
Rat	8	15	0, 0.001, 0.002, 0.003, 0.004, 0.005, 0.009,0.01 0.018, 0.02, 0.036, 0.041, 0.061, 0.072, 0.082, 0.102, 0.107, 0.122, 0.143, 0.163, 0.179, 0.204, 0.215, 0.245, 0.287, 0.326, 0.358, 0.43, 0.573, 0.653, 1.15	41 m

The same view is also reflected by the Safety Working Party (SWP) response to CHMP List of questions (see section on expert consultation for details).

The rat TD_{50} results in an AI level of **26.5 ng/day,** equal to **0.083 ppm** in a 320 mg valsartan tablet, associated with an excess lifetime cancer risk of 1 in 100,000 as indicated in the table below.

Table 7: NDEA amounts associated with a 1:100,000 excess lifetime risk in ng and ppm for maximum daily doses of sartans

API	max daily dose mg	NDEA AI ng	NDEA ppm
Valsartan	320	26.5	0.083
Losartan	150	26.5	0.177
Olmesartan	40	26.5	0.663
Irbesartan	300	26.5	0.088
Candesartan	32	26.5	0.828

Excess risk calculations

The CHMP agreed that the harmonic mean TD_{50} as calculated by the CPDB method should be used for the excess risk calculation approach in ICH M7(R1).

Calculations for AIs and excess risk are summarised in the tables below:

Table 8: Calculated excess theoretical cancer risk associated with NDMA intake

Point of departure NDMA	Dose (mg/kg/day)	TD_{50}: ÷ 50000 (ng/kg/day); $BMDL_{10}$: ÷ 10000 (ng/kg/day)	* 50 Kg (ng/day) = acceptable intake	* 25550 days (lifetime (70 years)	**Acceptable intake when taken over 6 years** ÷ 2190 days (6 years of valsartan exposure)	**Theoretical excess lifetime cancer risk** if taking 320 mg/day valsartan contaminated with 24.1 µg for 6 years	÷ 320 mg tablet (ppm)
TD_{50} rat liver tumours	0.096	1.92	96	2453 µg	1.12 µg/day	21.5:100,000 or approx. 1:5000 (0.02%)	0.3

Table 9: Calculated excess theoretical cancer risk associated with NDEA intake

Point of departure NDEA	mg/kg/day	TD_{50}: ÷ 50000 (ng/kg/day)	* 50 Kg (ng/day) = acceptable intake	* 25550 days (lifetime (70 years)	**Acceptable intake when taken over 4 years** ÷ 1460 days (4 years of valsartan exposure)	**Theoretical excess lifetime cancer risk** if taking 320 mg/day valsartan contaminated with 3.7 µg for 4 years	÷ 320 mg tablet (ppm)
TD_{50} rat liver tumours and other tumours	0.0265	0.53	26.5	677 µg	0.46 µg/day	8:100,000 (0.008%)	0.083

Cumulative excess cancer risk on co-exposure to NDMA and NDEA

Both compounds are assumed to be toxic mainly by the mutagenic action of highly reactive metabolites which alkylate DNA and form highly mutagenic DNA-adducts. It is assumed that DNA adducts add up in linear kinetics.

Adduct formation follows a linear kinetic and the risk is also considered to be additive. Cumulative risk can then be calculated by adding up the calculated single compound risk values. A potential worst case scenario would be an exposure to NDEA for 4 years (2011 – 2015) and NDMA exposure for 6 years (2012 – 2018). The cumulative theoretical excess risk would then be 29.5:100,000 or 1:3390 or 0.029%. This is equivalent to what was suggested in the SWP response to the CHMP List of Questions (see expert consultation section below) with using toxic equivalency by assigning toxic equivalency factors to the single compounds in a mixture.

Further considerations on alternative methods for calculation of theoretical excess cancer risk ($BMDL_{10}$)

Dose response curves of cancer studies are usually not linear but sub linear; this is also the case for the studies with NDMA. The TD_{50} is the well accepted conservative starting point recommended by ICH

M7(R1) for the calculation of the acceptable excess risk to calculate AIs for mutagenic and carcinogenic impurities and it is a well-recognized international standard.

However, this method is considered conservative and therefore may overestimate the real risk and not be the most appropriate one for realistic excess risk calculations. The $BMDL_{10}$ is considered a more realistic risk estimation, however, it still lacks an international harmonized calculation methodology and was therefore not considered suitable to calculate AIs.

The $BMDL_{10}$ is however discussed below using NDMA data for comparison:

The $BMDL_{10}$ represents an estimate of the lowest dose, which is 95% certain to cause no more than a 10% cancer incidence in rodents, as the point of departure for the calculation of excess cancer risk. The $BMDL_{10}$ is considered to represent a more realistic point of departure for risk estimations in low exposure scenarios, than a TD_{50} value.

Using the $BMDL_{10}$ for calculation of excess cancer risk is also outlined in ICH M7(R1) and this approach was the recommended approach in the expert consultation (see section 4).

Published $BMDL_{10}$ values for NDMA calculated for total liver tumours in male rats using data from Peto et al. (1991), either the complete data set or only part of it, and data from different sources, results in a range from 0.029 mg/kg/day (Zeilmaker et al., 2010, PROAST 17.9) to 0.062 mg/kg/day (Herrmann et al., 2015). A calculation with a recent version (version 65.2) of the PROAST (RIVM 2018) software developed by the RIVM resulted in a $BMDL_{10}$ of 0.043 mg/kg/day for all liver tumours.

$BMDL_{10}$ value of 0.062 mg/kg/day is based on liver cell tumours incidence as marker and therefore not completely comparable with the 0.029 mg/kg/day derived from total liver tumours. Therefore, the $BMDL_{10}$ of 0.043 mg/kg/day is used as the more comparable upper level of the $BMDL_{10}$ range.

Calculation of the theoretical excess risk of 1:100,000 is then done by dividing the $BMDL_{10}$ by 10,000 (10% or 0.1 x 100,000). Using 0.029 mg/kg/day as the lower and 0.043 mg/kg/day as the upper levels of the range, this results in a range of 2.9 to 4.3 ng/kg/day. For a 50 kg person this would be: **145 ng/day – 215 ng/day** corresponding to **0.45 – 0.67 ppm** in a 320 mg valsartan tablet.

According to the Haber's rule, using the $BMDL_{10}$ range from above (i.e.: 145 ng/day – 215 ng/day) this results in a lifetime acceptable dose associated with a 1:100,000 additional cancer risk of 3705 µg – 5439 µg. Dividing by 2190 results in **1.7 µg/day – 2.5 µg/day as AI over 6 years**.

This calculation resulted in a theoretical excess lifetime cancer risk in the range of 9.6 – 14:100,000 (0.0096% - 0.014%) for taking daily 320 mg valsartan contaminated with 24.1 µg NDMA (the mean NDMA value tested in a FP using API from ZH).

This calculated risk is slightly lower than the 0.02% (1:5000) calculated using the TD_{50} approach demonstrating that measures taken immediately on occurrence of this incident were sufficiently protective and also that the TD_{50} approach is not overly conservative compared to $BMDL_{10}$.

Calculations for AI levels and excess risk are summarised in the table below.

Table 10 Comparison of the TD_{50} and $BMDL_{10}$ approach to calculate theoretical excess lifetime cancer risks.

Point of departure NDMA	Dose (mg/kg/day)	TD_{50}: ÷ 50000 (ng/kg/day); $BMDL_{10}$: ÷ 10000 (ng/kg/day)	* 50 Kg (ng/day) = acceptable intake	* 25550 days (lifetime (70 years)	**Acceptable intake when taken over 6 years**	**Theoretical excess lifetime cancer risk**	÷ 320 mg tablet (ppm)
					÷ 2190 days (6 years of valsartan exposure)	if taking 320 mg/day valsartan contaminated with 24.1 µg for 6 years	
TD_{50} rat liver tumours	0.096	1.92	96	2453 µg	1.12 µg/day	21.5:100,000 (0.02%)	0.3
$BMDL_{10}$ rat liver tumours	0.029	2.9	145	3705 µg	1.7 µg/day	14:100,000 (0.014%)	0.45
$BMDL_{10}$ rat liver tumours	0.043	4.3	215	5493 µg	2.5 µg/d	9.6:100,000 (0.01%)	0.67

Assessment of additional nitrosamines other than NDMA and NDEA

As regards the additional nitrosamine impurities found or which can be potentially formed in valsartan, the following is highlighted:

- The valsartan N-nitroso impurity (Fig.4) , found only by one MAH in valsartan , is considered a non-mutagenic aromatic nitrosamine controlled as "unspecified" impurity at < 1000 ppm in valsartan drug substance. Negative results for valsartan N-nitroso impurity at Ames test appear reliable although no formal GLP-compliance was declared. Salmonella strains used are those indicated in ICH S2 guideline and are adequate to detect base-pair substitution, frameshift and cross-linking mutation mechanisms. Although the available evidence does not allow clearly concluding on a positive correlation between mutagenicity (Ames test) and carcinogenicity of alyphatic or aromatic nitrosoamines, the structural similarity between valsartan N-nitroso impurity and valsartan suggests a limited in vivo oxidative metabolism that would potentially lead to DNA alkylating impurities also for valsartan N-nitroso impurity.
- Three manufacturers reported that DIPNA (NDIPA, NDIA) and EIPNA (NEIPA. NIEA) can potentially be formed) due to the use of *N,N*-diisopropylethyl-N-ethylamine (DIPEA), a tertiary amine, in the synthesis. For both DIPNA and EIPNA, the daily intake limit and corresponding concentration of NDEA, calculated for the maximum valsartan daily dose authorized in the EU (320 mg), should be applied (i.e. 26.5 ng/day and 0.08 ppm, respectively). It is however noted that valsartan finished product batches manufactured using intermediates from one manufacturer are still within shelf life and are released in EU market. Thus CHMP recommends testing API batches contained in these products. using an adequate analytical method able to determine the two impurities, and a "reporting threshold" of 0.08 ppm. Overall, the same control approach applied for NDMA and NDEA (i.e. optimisation of synthetic process by adoption of strategies to mitigate risk of nitrosamine contamination, for example elimination of

the tertiary amine DIPEA, and specification limits) should also be applied for DIPNA and EIPNA in valsartan

- 4-(methyl)(nitroso)amino)butanoic acid (BMSA/NMBA) has been reported as a potential impurity in losartan from one manufacturer and was actually detected in Losartan batches of Hetero Labs. It can be formed during the synthesis of losartan while using sodium nitrite and N-methylpyrrolidone. For NMBA, a carcinogenicity study in rats is listed in CPDB (Hasegawa et al. 1998) with a TD50 of 982 µg/kg/d. This leads to a provisional calculation of an AI of 982 ng/day for a 50 kg human associated with a 1:100,000 excess lifetime cancer risk. There are currently contradictory mutagenicity data in bacteria (Ames negative and positive results in different tests). Therefore, it can currently not be concluded whether NMBA is a mutagenic or non-mutagenic carcinogen. As a precaution, NMBA should currently be considered as a mutagenic carcinogen like NDMA and NDEA for the time being. However, due to the limitations of the available carcinogenicity study and limited other toxicological data, additional data and analyses might be needed to define an AI. A precautionary approach like for DIPNA and EIPNA is recommended in this situation.

Conclusion on Non-clinical aspects

Risk assessment for patients previously exposed to NDMA /NDEA

As outlined above the calculation of AI levels of mutagenic impurities follows the internationally accepted guidance of ICH M7(R1). AIs are considered as those associated with an excess lifetime cancer risk of not more than 1:100,000. The starting point of the calculation is the data from lifetime carcinogenicity studies in animals. The calculation is based on the conservative assumption of a linear dose response relationship for mutagenic carcinogens like NDMA and NDEA. It extrapolates into very low exposure levels where it is impossible to measure effects experimentally. It is considered to very likely overestimate the real risk and is therefore precautious and conservative with regard to patient safety. Using this approach, described in detail above (section 3.3) the calculated theoretical excess lifetime cancer risk for patients is shown in the table below:

Table 11: Calculated theoretical excess lifetime cancer risk for patients

	NDMA exposure for 6 years with 24.1 µg/d	NDEA exposure for 4 years with 3.7 µg/d	Co-exposure to NDMA 24.1 µg/d and NDEA 3.7 µg/d for 4 years plus additional exposure to NDMA 24.1 µg/d for 2 years
excess life time cancer risk	21.5 in 100,000 or 0.02 %	8 in 100,000 or 0.008 %	29.5 in 100,000 or 0.03 %

For patients exposed for 6 years to NDMA-contaminated valsartan assuming a 1:1 transfer of the impurity from API to finished product and a mean NDMA content of 24.1 µg in a 320 mg tablet, the theoretical excess risk of cancer during lifetime is calculated to be 21.5 in 100,000. This is approximately 0.02%. For patients exposed for 4 years to NDEA-contaminated valsartan assuming a 1:1 transfer of the impurity from API to finished product and a mean NDEA content of 3.7 µg in a 320 mg tablet, this theoretical excess risk is calculated to be 8 in 100,000 (0.08%). The excess risk in patients co-exposed to both NDMA and NDEA for 4 years and NDMA alone for 2 years is calculated to be 29.5 in 100,000 or 0.03%.

Compared to the overall risk of cancer during lifetime for the EU population (e.g.in Germany reportedly 50.3 % in men and 43.5 % in women; in Italy 62% in men and 59% in women) the theoretical additional risk due to the highest levels reported of NDMA/NDEA in some valsartan batches is considered very low.

Target organ(s) of NDMA and NDEA in humans are currently unknown. In animal experiments across species the primary target organ is liver. Additionally, tumours were observed in oesophagus, kidney, vasculature system, gastrointestinal tract and lung with either NDMA and/or NDEA. However, extrapolation to potential target organs for carcinogenicity in humans is highly uncertain. This is also the conclusion of the SWP. An overview is given in the table below.

Table 12 Overview of different tumour entities observed in animal studies

NDMA	**NDEA**
# Rat [CPDB; across all rat studies[1]] • *Liver (M & F)* • *Vascular system (M & F)* • *Kidney (M)* • *Lungs (M)* • *Testes (M)* # Rat [CPDB; Peto study (1991)] • *<u>Liver - reported tumour types</u>* o *Neoplasm of liver cell, bile duct, mesenchyme, Kupffer cell (M & F), TD50: 0.042-0.087mg/kg/d* o *Intrahepatic bile duct tumour (M & F), TD50: 0.075-0.31mg/kg/d* o *Intrahepatic bile duct tumour, benign (M & F), TD50: 0.076-0.31mg/kg/d* o *Hepatocellular tumour (M & F), TD50: 0.145-0.157mg/kg/d* o *Hepatocellular carcinoma (M & F), TD50: 0.218-0.238mg/kg/d* o *Mesenchymal hemangio-sarcoma, -pericytoma, or -endothelioma, malignant (M & F), TD50: 0.712-0.914mg/kg/d*	# Rat [CPDB**;** across all rat studies[1]] • *Liver (M & F)* • *Oesophagus (M & F)* • *Kidney (M)* • *Oral cavity (F)* • *Stomach (F)* • *Vascular system (M)* # Rat [CPDB; Peto study (1991)] • *<u>Liver - reported tumour types</u>* o *Neoplasm of liver cell, bile duct, mesenchyme, Kupffer cell (M & F), TD50: 0.050-0.052mg/kg/d* o *Intrahepatic bile duct tumour (M & F), TD50: 0.372-0.561mg/kg/d* o *Intrahepatic bile duct tumour, benign (M & F), TD50: 0.419-0.562mg/kg/d* o *Hepatocellular tumour (M & F), TD50: 0.062-0.092mg/kg/d* o *Hepatocellular carcinoma (M & F), TD50: 0.105-0.136mg/kg/d* • *<u>Oesophagus - reported tumour types</u>* o *More than one tumour type (“mix”), TD50: 0.095-0.203mg/kg/d* o *Malignant tumour (M & F), TD50: 0.236-0.729mg/kg/d*

NDMA	**NDEA**
# Mouse [CPDB; across all mouse studies[1]] • *Nervous system (M & F)* • *Liver (M)* • *Lungs (F)* # Mouse [IARC, 1978]. In one study (Clapp & Toya, 1978), drinking water exposure gave liver and lung tumours at 0.4mg/kg/d. • Liver tumours • Lung tumours • Kidney tumours	# Mouse [CPDB; across all mouse studies[1]] • No reported studies in CPDB. # Mouse [IARC, 1978]. Mice given a dosage of 2-13 mg/kg/d tend to approach 100% tumour incidence. • Liver tumours (various studies) • Lung tumours • Oesophagus tumours • Forestomach tumours • Kidney tumours # It can be noted that NDEA is used as a model hepatocarcinogen that is used in numerous mechanistic mouse studies of hepatocarcinoma.
# Cynomolgus [CPDB; Thorgeirsson et al (1994)] • No cancer-related outcomes • Signs of hepatotoxicity at end of life.	# Cynomolgus [CPDB; Thorgeirsson et al (1994)] • *Liver (oral exposure)* o *Hepatocellular carcinoma (M & F), LOAEL: 2.08mg/kg/d (1-dose study)* • *Liver (i.p.)* o *Hepatocellular carcinoma (M & F), LOAEL: 0.0036mg/kg/d, TD50: 0.0036mg/kg (5-doses with few animals in low and middle doses)*
# Rhesus [CPDB; Thorgeirsson et al (1994)] • No cancer-related outcomes • Signs of hepatotoxicity at end of life.	# Rhesus [CPDB; Thorgeirsson et al (1994)] • *Liver (oral exposure)* o *Hepatocellular carcinoma (M & F), LOAEL: 2.62mg/kg/d (1-dose study)* • *Liver (i.p.)* o *Hepatocellular carcinoma (M & F), LOAEL: 0.0080mg/kg/d, TD50: 0.0027mg/kg (5-doses with few animals in low and middle doses)*

The impact of NDMA and NDEA on human health is currently only extrapolated from animal studies. However, as the mechanisms outlined above are also present in humans and *in vitro* data in human cells are not significantly different from those in animal cells, it is prudent to assume that effects observed in animals could also potentially occur in humans. A full risk assessment for patients exposed to NDMA and/or NDEA is not possible as the real extent of exposure of patients is in principle

impossible to establish, as data of finished products used by each individual patient would be necessary.

Provisional interim limits for future batches

Based on the same TD_{50} data in rats outlined above, compound specific AI levels associated with a theoretical excess cancer risk of 1:100,000 when exposed daily for life time have been calculated according to ICH M7 (R1). The limits are given in the table below together with corresponding ppm values in the maximum daily dose of each sartan:

Table 13 Acceptable Intake (AI) levels and corresponding concentrations of NDMA and NDEA per active substance for their maximum daily dose authorised in the European Union.

API	Max. daily dose (mg)	NDEA AI(ng/day)	NDEA Corresponding concentration level (ppm in API)	NDMA AI(ng/day)	NDMA Corresponding concentration level (ppm in API)
Valsartan	320	26.5	0.082	96.0	0.300
Losartan	150	26.5	0.177	96.0	0.640
Olmesartan	40	26.5	0.663	96.0	2.400
Irbesartan	300	26.5	0.088	96.0	0.320
Candesartan	32	26.5	0.820	96.0	3.000

These levels have been used for decision making at Member State level in case of detection of NDMA and NDEA during the procedure, and have been referenced by MAHs and API manufacturers in their responses when presenting analytical results. The CHMP considered that these limits could be used during a transition phase during which companies will have to carefully review, and if warranted, change their manufacturing processes to further reduce formation of nitrosamines.

Other nitrosamines

<u>DIPNA and EIPNA</u>

Since DIPNA and EIPNA share the same toxicological profile of NDEA, the same control approach applied for NDMA and NDEA (i.e. optimisation of synthetic process by adoption of strategies to mitigate risk of nitrosamine contamination, for example through the elimination of the tertiary amine DIPEA, and application of specification limits) should also be applied for DIPNA and EIPNA.

Valsartan N-nitroso impurity With regard to the formation of (S)-2-(((2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)(nitroso)amino)-3-methylbutanoic acid reported by one manufacturer in valsartan CHMP agrees that this is a non-mutagenic aromatic nitrosamine and it is acceptable that it is controlled as "unspecified" impurity at < 1000 ppm in API.

NMBA

With regard to the potential formation of 4-(methyl)(nitroso)amino)butanoic acid (BMSA/NMBA) during the synthesis of losartan while using sodium nitrite and N-methylpyrrolidone, an AI level based on animal carcinogenicity data (CPDB) 982 ng/day has been calculated provisionally using the same methodology as for NDMA/NDEA. For NMBA, a carcinogenicity study in rats is listed in CPDB (Hasegawa et al. 1998) with a TD_{50} of 982 µg/kg/d. This corresponds to an AI level of 982ng/d.

There are currently contradictory mutagenicity data in bacteria (AMES negative and positive results in different tests). Therefore, it can currently not be concluded whether it is a mutagenic or non-mutagenic carcinogen. As a precaution, it should currently be considered as a mutagenic carcinogen like NDMA and NDEA. Due to the limitations of the available carcinogenicity study and limited toxicological data, additional data and analyses might be needed to define an AI. A precautionary approach like for DIPNA and EIPNA is recommended in this situation.

Other potential nitrosamines

The toxicology assessment of nitrosamines not detailed in this report should follow the same principles that have been established for NDMA and NDEA, unless otherwise justified.

2.4. Clinical aspects

It is important to consider that the target organs of NDMA/NDEA toxicity and cancer may differ between species. In rats, used for calculating the theoretical excess risk in humans, the main target organ is liver, which is also a target organ in other species. Besides liver, the organs affected vary across species. There are currently too limited data on NDMA/NDEA target organs in humans exposed chronically to doses of nitrosamines exceeding the occupational exposure. The limited epidemiological data available in humans point to an increase in colorectal cancer and in one study a correlation of NDMA/NDEA exposure with pancreatic cancer incidence was reported (Knekt et al. 1999, Loh et al. 2011, Zheng et al. 2018). In those studies, excess exposure to nitrosamines in the range of several hundreds of nanograms was associated with increased cancer risks. These data however are derived from virtual extrapolation of NDMA and or NDEA exposure calculated via food intake surveys and it is questionable whether the findings are really attributable to NDMA or NDEA. Parenteral exposure of monkeys to NDMA leads to severe liver toxicity and parenteral and oral exposure to NDEA leads to liver tumours; however, valid data for target organ(s) of oral NDMA or NDEA exposure of humans are not available.

A first EU cohort study in patients potentially exposed to NDMA contaminated valsartan was performed in Denmark by Pottegard et al. (2018). The study did not identify an increase in total cancer cases in NDMA-exposed patients (hazard ratio for overall cancer was 1.09 (95% confidence interval 0.85 to 1.41). For single cancer outcomes, increases in risk were observed for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), although with wide confidence intervals that included the null. The wide confidence intervals suggest that the study population was too small (final cohort: N= 5150) and/or the observed events too few and therefore no final conclusion can be drawn on whether the observations are a chance finding or represent a real

effect. Although the preliminary study data from this nationwide registry provide some reassurance, the mean follow up period in that study is only 4.6 years and therefore far too short to assess alifetime cancer risks. Continuous periodical surveillance of patients in such registry-based studies may potentially be helpful to provide further evidence for the absence or presence of any long term effect. The study by Pottegard et al. (2018) has focused on NDMA contaminated valsartan and did not focus on patients potentially co-exposed to NDMA and NDEA.

In October 2011, EMA concluded a referral procedure according to Article 5(3) of Regulation (EC) No 726/2004 on Angiotensin II (type-1) receptor antagonists and risk of cancer (EMEA/H/A-5(3)/1274). The CHMP concluded in the above referral that the evidence collected at that time from clinical trials and epidemiological studies did not support a signal of increased cancer risk associated with ARBs. Therefore, it is unlikely that ARBs as such would enhance a nitrosamine-associated cancer risk.

Currently, it is not possible to conclude on any risk minimization measures exposed patient would benefit from. The very small theoretical excess risk calculated based on animal studies has to be balanced against the risks of measures to monitor patients such as colonoscopy or gastroscopy that may exceed the theoretical excess cancer risk. For example, a recent review has estimated risks of perforation of 4 per 10,000 (95% confidence interval, 2-5) and major haemorrhage of 8 per 10,000 (95% confidence interval, 5-14) with screening colonoscopy (Lin et al. JAMA 2016). In addition, advancing age, comorbidity and use of anticoagulants were found to be strongly associated with both gastrointestinal and non-gastrointestinal complications. Furthermore, the target organ(s) of NDMA/NDEA toxicity in humans are still not sufficiently clear.

Therapeutic use of ARBs

Arterial hypertension

Concerning arterial hypertension in adults in general all of the ARBs (for detailed indications see introduction section) are mutually exchangeable provided specific dosing recommendations e.g. in case of renal failure are taken into consideration. In the adult population there is a variety of medicinal products from other classes that can serve as therapeutic alternatives (e.g. ACE inhibitors, beta blockers, calcium channel blockers, diuretics). A switch between antihypertensive products requires medical supervision. In patients requiring combination therapy or with severe hypertension therapy special attention is necessary to find an appropriate alternative.

In the paediatric population with the exception of irbesartan all of the tetrazol-ARBs can be used and mutually exchanged whereas for none of the non-tetrazol ARB an indication or dosing recommendation has been approved. Azilsartan and Telmisartan are indicated for the treatment of essential hypertension in adults only. For Eprosartan the indication does not contain an age restriction, but the use in the paediatric population is not recommended in the absence of data. Besides tetrazol ARBs there are a number of different options, including ACE inhibitors, beta blockers, long acting calcium antagonists, and diuretics for paediatric patients. In summary, drugs from all of these classes can be considered as an alternative to treat arterial hypertension in the paediatric population.

Heart failure

Candesartan, Losartan and valsartan are indicated for the treatment of patients with heart failure. For most of the patients ACE inhibitors or sacubitril-valsartan are valid therapeutic alternatives.

Treatment of renal disease in adult patients with hypertension and type 2 diabetes as part of the antihypertensive therapy

Irbesartan and losartan are indicated. In addition, ACE inhibitors may be considered as therapeutic alternatives if needed.

Treatment of symptomatic heart failure or asymptomatic left ventricular dysfunction after acute myocardial infarction (valsartan); reduction of strokes in adult patients with hypertension and left ventricular hypertrophy (losartan).

ACE inhibitors are indicated for the treatment of symptomatic heart failure. ACE inhibitors may be considered as therapeutic alternatives if needed.

Conclusion on clinical aspects

In view of the very low theoretical excess cancer risk, the fact that the risk estimation is based on a very conservative approach, the absence of an increase in overall cancer cases in a preliminary clinical cohort study, the risk of complications of invasive screening methods and the uncertainty of the target organ(s) of NDMA/NDEA toxicity in humans, the CHMP does not recommend additional monitoring of previously exposed patients.

ARBs are important for the treatment and prophylaxis of severe cardiovascular diseases and are in wide-spread use in the EU. Alternative medicinal products in the therapeutic areas (arterial hypertension, heart failure, cardiovascular prophylaxis, renal disease in special populations) are available as needed. Patients should not stop their sartan medicine without speaking to their doctor since it is much riskier to stop taking any sartan medicines than the risk related to potential nitrosamine impurities.

3. Expert consultation

Ad-hoc expert consultation

Following a request from CHMP, an ad-hoc expert consultation was convened on 19 July 2018 to provide advice on approach to be used in the calculation of the risk to develop cancer in patients who were exposed to NDMA contaminated valsartan-containing medicinal products.

The experts discussed the relevant toxicological data available for NDMA, the models available for estimation of risk and, relevant study endpoints and best choice of point of departure for risk estimations and agreed on the following points:

- The most relevant toxicological risk with NDMA exposure is carcinogenicity
- No reliable epidemiological data for humans are available to calculate excess risk levels
- The most relevant endpoint for excess risk calculation is cancer in animals
- The scientifically most appropriate study for use for excess risk calculations is the extensive study in rats by Peto et al. (1991)
- The Bench Mark Dose Lower bound (BMDL) model is considered the scientifically most accepted model for analysis cancer studies
- As starting point, the Bench Mark Dose Lower bound with a Benchmark response of 10% (BMDL10 for tumours, including all liver tumours) should be used. This is the considered the bench mark response mostly used to assess cancer studies.
- NDMA concentrations in finished product are more precise for risk assessment

- Realistic worst case scenarios should be use for estimation of total patient exposure
- Environmental background exposure with nitrosamines.

The advice provided by the experts was considered by the CHMP.

Working Party consultation

Safety Working Party (SWP)

Consultation of the SWP took place in November 2018 and a summary of the conclusions is provided below:

The SWP approach towards the risk assessment of NDMA and NDEA contaminations in sartan containing products is based on the praxis established by ICH M7(R1). This means calculating safety limits via a so called linear extrapolation method (a highly conservative approach). These limits are considered safe based on today's generally regulatory accepted view that a theoretical additional contamination-linked risk of 1 cancer in 100,000 exposed subjects is acceptable.

Question 1: *The points of departure and methodology for calculating acceptable intake and excess carcinogenicity risk for NDMA and NDEA*

Two possible PoD approaches (TD_{50} and $BMDL_{10}$, in line with ICH M7(R1) recommendations) are discussed and the TD_{50} was selected as the appropriate PoD approach and identifies rat as the most appropriate animal species for the source data for the TD_{50}. SWP then recommended harmonic mean TD_{50} value (the TD_{50} across several animal studies of the same species) with 0.096mg/kg/day for NDMA and 0.0265mg/kg/day for NDEA.

Question 2: *The most appropriate methodology to estimate the cumulative excess carcinogenicity risk from exposure to both NDEA and NDMA*

Based on the mechanistic similarity underlying NDMA and NDEA hepato-carcinogenicity, a very simplified Toxic Equivalency Factor-Toxic Equivalency (TEF-TEQ)-like calculation approach is proposed for combining the risk estimations from both impurities. This approach regards an Environmental toxicology methodology used to make risk assessments of mixtures containing different classes of dioxins. The present cumulative risk assessment is based on that one uses the cumulative life time dose approach (discussed answer to question 1) together with the rat PoD values to select the most potent nitrosamine (NDEA if one uses harmonic mean TD_{50}) in order to convert the NDMA impact into an equivalent NDEA impact. It should be noted that a requirement is that one uses the same PoD approach (i.e. TD_{50}) for both nitrosamines.

Q3: *What is the adequacy of Ames test to screen mutagenic impurities in the APIs in the scope of this referral?*

The SWP does not consider that the Ames test can be used in this capacity. While there are some nitrosamine sensitive Ames tests (e.g. alkyl-transferase deficient S. typhimurium strains YG7100, YG7104 and/or YG7108) available that make nitrosamine studies possible, it is unlikely that using those for API batch screening will be meaningful.

Q4: *The species differences in target organs for NDMA/NDEA and potential target organs in humans?*

The SWP considers that any such extrapolation is highly uncertain. That being said, based on the most common nitrosamine-induced tumour across several animal species, the liver seems to be the most high-ranked possibility.

Q5: ***Can a safe limit for daily NDMA or NDEA intake be identified for sartan-containing medicinal products or is it considered necessary to avoid these impurities altogether?***

The European assessment procedures for mutagenic impurities in pharmaceuticals follow the ICH M7(R1) guideline. As outlined in ICH M7(R1), it is possible to define acceptable levels for mutagenic impurities based on an acceptable theoretical risk of 1 additional cancer among 100,000 subjects exposed life-long to the impurity, and which may be regarded as safe. According to the ICH M7(R1) guideline, NDMA and NDEA are known mutagenic carcinogens (class 1), for which the default TTC of 1.5 µg/day is not acceptable, and therefore compound specific limits are considered necessary.

Regarding the answer to this question, there are two different opinions within the SWP focussing on risk minimisation (view 1) and risk avoidance (view 2):

I) Risk minimisation (view 1): The established AI approach as outlined in ICH M7(R1) utilizes a highly conservative risk estimation procedure which is considered appropriate as long as levels are kept below this threshold. There is no reason to diverge from the risk/benefit balance regulatory practices for handling mutagenic impurities. The reason is that there is no factual evidence that NDMA and NDEA are fundamentally different from other mutagenic carcinogens, which are covered by the TTC framework in ICH M7(R1), besides being more potent. This higher potency is handled by defining compound specific thresholds based on carcinogenicity data and by linear extrapolation. There is no necessity for a “no threshold” approach.

II) Risk avoidance (view 2): This opinion states that manufacturing processes with any potential nitrosamine generating step should be avoided. This opinion is based on the view that any level of nitrosamine exposure of the public comes with a risk and there is no need to establish AIs for impurities in the first place as the contamination risk is considered to be avoidable by avoiding certain manufacturing processes.

It should also be noted that while avoidance of a nitrosamine contamination via medicinal products would be preferable, considering the background exposure (from food, water etc.) of nitrosamines, it is impossible to avoid the intake of such impurities/substances altogether. On the other hand, while the European Food Safety Agency (EFSA)is active in reducing the food-mediated intake of nitrosamines by expressing recommendations in preparing food, the medicinal products should not add to the exposure in patients.

Both views have in common that they focus on the safety of the patients to be treated with pharmacotherapy to lower blood pressure and related issues.

Quality Working Party (QWP)

A Consultation of the Quality Working Party took place in December 2018 and a summary of the conclusions is provided below:

Q1) The potential root causes for contaminations of NDMA and NDEA. Please comment on the assessment of root causes identified by companies as appropriate.

Companies whose APIs were contaminated with NDMA or NDEA (or other *N*-nitrosamine impurities) were requested to provide a thorough root cause analysis in the latest round of questions. Whilst it seems clear that the root cause of the problem is the combination of secondary amines and $NaNO_2$ + acid, the source of the secondary amine is crucial to any mitigation strategy. Therefore, experimental data from companies is expected in order to determine the source of the secondary amine. Furthermore, companies should identify additional process parameters which are implicated in *N*-

nitrosamine formation (e.g. temperature, stoichiometry, time, work up procedure, etc.). Conclusive data-based assessment of the root cause can only be done once the responses are received.

Several root causes have been discussed. The list is unlikely to be exhaustive. The source of *N*-nitrosamines could be down to one root cause, or a combination of several, which could also help explain overall variability in contamination.

Q2) Potential mitigation measures for future valsartan, losartan, olmesartan, irbesartan, candesartan manufacturing and process changes in relation to the formation *N*-nitrosamines. Provide input into assessment of proposed CAPAs in cases where nitrosamines were identified.

To prevent N-nitrosamine formation, it is best to avoid use of $NaNO_2$ until the API has been separated from the aqueous phase during work up. It should be noted that the purpose of the $NaNO_2$ is to quench sodium azide, which is itself highly reactive and a genotoxic impurity. Therefore, it should be demonstrated using suitably sensitive and validated analytical methods that azide is adequately purged when using the proposed revised process before that source of API can be accepted. The same applies to any process where azide is used, especially when azide residues haven't been quenched. Batch data demonstrating absence in the API should be provided. Further assessment is only possible on provision of additional data from the company. Furthermore, if $NaNO_2$ is being used to quench azide away from the API, then solvents from this step should not be recovered and used in any process unless the risk of contamination with *N*-nitrosamines is suitably mitigated.

Strategies which companies could adopt to mitigate risk of nitrosamine contamination include:

- the use of alternative reaction conditions where the possibility of *N*-nitrosamine contamination is avoided completely. This could involve using different solvents (i.e. not amides such as DMF, DMA, NMP), different bases without secondary/tertiary amines (e.g. inorganic bases), or more hindered and thus less reactive amine bases;
- Change the order of reactions, introducing the tetrazole moiety at an earlier step – this gives more opportunity for purge of *N*-nitrosamines through subsequent synthesis steps and purification operations. It is good practice to carry out steps involving mutagens early in a synthetic sequence for exactly this reason;
- Off-line quenching of azide, following separation of aqueous and organic layers. This is the strategy proposed by ZHP. However, it remains to be seen how the azide is partitioned between aqueous and organic phases, and how much is left, following washing, in the product layer;
- Replacement of $NaNO_2$ with alternative quenching agents (for azide destruction), e.g. sodium sulphite, sodium thiosulfate etc.;
- Additional purification steps to purge nitrosamine impurities (e.g. further crystallisations). It would need to be demonstrated that the *N*-nitrosamine impurity was sufficiently purged (dependent on input from SWP, the answer to question 3 below, and the capability of analytical methods (LoD, LoQ)) and this should be demonstrated for the API. If there is any potential for the presence of an *N*-nitrosamine impurity, a limit has to be set in the API (for transparency over life-cycle). It is also suggested that the relevant Ph. Eur. monographs may need updating with relevant limits for *N*-nitrosamine impurities. A production statement will be included in each relevant sartan monograph warning of the potential contamination with *N*-nitrosamine impurities. In addition, a general monograph will be published containing an analytical method for quantification of relevant *N*-nitrosamines;

- The use of recovered solvents from steps where there is a risk of *N*-nitrosamine formation (either as part of the API process or as part of the recovery process) should be avoided, or it should be demonstrated that *N*-nitrosamines are adequately purged (i.e. they should be limited by specification). This applies particularly to the final step;
- Control of raw materials that may introduce nitrite (NO_2^-) or *N*-nitrosamines. Examples of this are e.g. sodium azide, solvents and water;
- One MAH has claimed that $NaBH_4$ or strong acid can be used to destroy *N*-nitrosamines although experimental evidence is missing. There are further suggestions that *N*-nitrosamines can be degraded by exposure to UV light. Such treatments could be considered as methods of removing *N*-nitrosamine impurities although the active substance (or intermediate) would have to be stable under those conditions.

As an alternative to not use nitrites, risk of *N*-nitrosamine formation can be mitigated by other means. However, in that case the demonstration of absence (or a sufficiently low level) of *N*-nitrosamines would have to be demonstrated in the API and included in the specification. The risk is lower when the formation of *N*-nitrosamines is avoided in the first place.

ICH M7 option 4 or skip testing would not generally be appropriate given the potential risks of contamination, the batch to batch variability observed so far, and considering the very low acceptable levels of such impurities (i.e. the capability of analytical methods to determine that only a negligible amount of these impurities is present).

Given the various potential sources of *N*-nitrosamines impurities, ICH M7 option 1 (i.e. a limit in the API specification) would generally be the most appropriate control method.

In order for the MAHs to take responsibility for their finished product(s), including responsibility for the quality of the drug substance used in the finished product, they should ensure (via quality agreements) that it and the finished product manufacturer have access to relevant information from the active substance manufacturer concerning potential formation and presence of N-nitrosamine impurities, as well as potential cross-contamination, regardless of whether a limit has been established or not for these impurities.

Q3) Input into the need to set limits for NDMA and NDEA or whether, given the potency, the proposed TTC, and the capability of analytical methods, no amount of *N*-nitrosamine would be acceptable.

The outcome of the discussion at QWP on this topic was not fully conclusive. The majority favoured applying a limit. Some members underlined that such a limit approach is questionable for compounds like NDMA / NDEA, which may cause unacceptable toxicities. Therefore, it was concluded that a specification limit could only be applied if Safety Working Party (SWP) would agree that such a limit could be defined. An additional question to SWP was adopted by CHMP as follows:

> "Can a safe limit for daily NDMA or NDEA intake be identified for sartan-containing medicinal products or is it considered necessary to avoid these impurities altogether?"

The ICH M7(R1) states that "some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens referred to as the "cohort of concern", comprises aflatoxin-like-, *N*-nitroso-, and alkyl-azoxy compounds." It goes on to say that "compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like-, N-nitroso-, and alkylazoxy structures. If these compounds are found as impurities in pharmaceuticals, acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline.

Although the principles of this guideline can be used, a case-by-case approach using e.g., carcinogenicity data from closely related structures, if available, should usually be developed to justify acceptable intakes for pharmaceutical development and marketed products."

This suggests that setting a limit could be possible if such a limit is set based on compound-specific toxicity data, which is available for both NDMA and NDEA.

The proposed limits for valsartan of 0.3 ppm (NDMA) and 0.08 ppm (NDEA) have been extrapolated, using conservative methodology, from compound-specific animal toxicological data. Similarly, limits for NDMA and NDEA have been tentatively assigned, based on the maximum daily dose of each sartan medicine (Tab).

Table 14: Acceptable Intake (AI) levels and corresponding concentrations of NDMA and NDEA per active substance for their maximum daily dose authorised in the European Union.

API	Max. daily dose (mg)	NDEA AI (ng/day)	NDEA Corresponding concentrationI (ppm in API)	NDMA AI (ng/day)	NDMA Corresponding concentration level (ppm in API)
Valsartan	320	26.5	0.082	96.0	0.300
Losartan	150	26.5	0.177	96.0	0.640
Olmesartan	40	26.5	0.663	96.0	2.400
Irbesartan	300	26.5	0.088	96.0	0.320
Candesartan	32	26.5	0.820	96.0	3.000

In addition, if there is any potential of formation of *N*-nitrosamines in the process itself or in the process of recycling materials or originating from the environmental sources it would be safer to have a test and acceptance criteria in the specifications of the corresponding active substances.

Overall, QWP's opinion based on information currently available is that a limit for a given *N*-nitrosamine should be set in the specification of the API, or an intermediate where justified, if there is a risk of it being present. The risk of cross-contamination from e.g. recovered solvents should be considered as part of this risk. The limit in the specification is dependent on input from SWP and toxicology experts. Given the variability that has been seen in the content of *N*-nitrosamines in affected sartans, the validity of the sampling scheme will need to be rigorously demonstrated.

A consultation of the QWP (core team) in January 2019 focused on the definition of a limit which is based on analytical method capability. In summary, there was general consensus that using the LoD as a specification limit was not technically feasible due to the risk of false negative results and that if a technical limit was to be used, then it should be based on the LoQ, which would be used to derive a threshold. It was emphasized that neither LoD or LoQ are constant values and can change over time and depending on equipment, labs, personnel, sample preparation and many other factors. Therefore, companies should be developing their methods to be sensitive enough to meet the proposed 0.03 ppm threshold. In addition, it was proposed to request EDQM to develop a general analytical method and publish it in Ph. Eur.

In addition, QWP generally agreed that synthetic routes which have a risk of generation of *N*-nitrosamines should be avoided by first intent. It was also agreed that given the different sources of impurities, a limit in API specification is required.

4. Benefit-risk balance

4.1. Benefit-risk balance assessment

Sartan-containing medicinal products are important treatment options of serious or potentially serious conditions such as hypertension or certain heart or kidney diseases. Efficacy and safety of sartan-containing medicines in these indications are *per se* well-established and are not questioned in this referral. The key issue of this referral concerns the detection of *N*-nitrosamine (esp. NDMA and/or NDEA) contaminations in sartans, the resulting potential long-term risk to patients and measures to minimise as much as possible these contaminations.

Nitrosamines are chemically simple molecules and can be formed in pharmaceutical manufacturing steps whenever there is a presence of a secondary (or tertiary) amines and nitrites, usually in acidic conditions. This is the background to the current referral procedure. However, it should be noted that nitrosamines can also be formed in many other situations, including in biological processes.

NDMA and NDEA are two of the most potent mutagenic carcinogens known. As soon as the problem of nitrosamine-contamination became known, immediate, precautionary measures were taken by competent authorities across the EU such as recalls of affected batches from pharmacies. Initially, this was only necessary for valsartan containing APIs from few manufacturers but later also for some other sartans with a tetrazole ring.

Assessment of the excess risk of cancer

The impact of NDMA and NDEA on human health is currently only extrapolated from animal studies. However, as the DNA damage mechanisms documented in these studies are also relevant in humans and *in vitro* data in human cells are not significantly different from those in animal cells, it is prudent to assume that effects seen in animals may also occur in humans after exposure to sufficiently large amounts of these nitrosamines.

In addition to NDMA and NDEA, other *N*-nitrosamines have been detected in a few sartan-containing medicinal products. Risks resulting from multiple exposures are considered to add up in patients as mutagenic carcinogens are currently considered as summation toxins.

The ICH M7(R1) guideline sets out principles for determining acceptable limits for mutagenic / DNA-reactive impurities. The determination of an acceptable intake (AI) is based on extrapolation of carcinogenic risk from rodent carcinogenicity data, as the dose resulting in one cancer case among 100,000 individuals exposed for a life-time to the impurity. *N*-nitrosamines belong to a "cohort of concern" compounds, for which the guideline states "*Compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like-, N-nitroso-, and alkylazoxy structures. If these compounds are found as impurities in pharmaceuticals, acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline. Although the principles of this guideline can be used, a case-by-case approach using e.g., carcinogenicity data from closely related structures, if available, should usually be developed to justify acceptable intakes for pharmaceutical development and marketed products*".

For these reasons, *N*-nitrosamine impurities in pharmaceuticals such as sartans intended for long-term use should be reduced as much as possible.

A full risk assessment for patients previously exposed to NDMA and/or NDEA impurities in sartans, especially valsartan which was found to contain the highest nitrosamine contamination, is not possible as the real extent of exposure of patients is unkown. For an individual risk assessment, data on the exact finished products and batches used by each individual patient would be necessary. Thus, the risk

assessment is based on a potential worst case scenario, which would be a partially combined exposure to the highest levels of NDEA for 4 years (2011 – 2015) and to NDMA for 6 years (2012 – 2018) reported from a sartan, resulting in a cumulative theoretical excess cancer risk of 29.5:100,000 or 1:3390 (0.029%) when extrapolated from the above mentioned rat studies according to ICH M7(R1). Compared to the lifetime cancer risk in the European population of approximately 50%, this additional risk is considered to be very low.

Measures to mitigate the risk

Appropriate regulatory actions (such as quarantine or batch recalls) have been taken where relevant.

Additional measures are needed to minimise prospectively the reoccurrence of such contamination.

Based on all available data, the above conclusions on quality, non-clinical and clinical aspects , the CHMP requires the following:

1. Obligatory risk assessments to be performed for manufacturing processes of the drug substances in order to evaluate the theoretical risk of *N*-nitrosamine formation and contamination

2. Modifying manufacturing processes, where necessary, to minimise contamination as much as possible.

3. Implement a control strategy to detect and control *N*-nitrosamine impurities in the API (or intermediate, if justified).

Specifically, CHMP considered that NDMA and NDEA limits should be as low as technically possible. In this regard, a LoQ of 0.03 ppm for NDMA and NDEA would be achievable according to the available data on analytical methods. This limit is considered a sufficiently robust threshold for APIs that can technically be reached. In comparison to the AI levels calculated based on ICH M7(R1) using non-clinical toxicology, it is possible to generate additional safety factors ranging from 2.73 – 27.3 for NDMA and 10.0 – 100 for NDEA, by defining 0.03 ppm as the common technical target limit for NDEA and NDMA in tetrazole sartan APIs. The underlying concept of the proposed approach is to keep the amount of *N*-nitrosamine impurities as low as possible, irrespective of type of sartan or dose.

The limit of 0.03 ppm for NDMA and NDEA will be enforceable after a transitional period of 2 years from the notification of the Commission Decision. During this time period, MAHs and manufacturers are requested to introduce relevant changes to the manufacturing processes of the drug substances, as well as develop appropriate analytical methods while ensuring adequate supply of the market for these essential medicinal products. An interim limit based on AIs according to principles in ICH M7(R1) using toxicology data are set in order to control these impurities in the meantime to an acceptable level.

Whilst the measures are focused on NDMA and NDEA, the principles described in this assessment in terms of toxicology assessment, control strategy and changes to the manufacturing processes for drug substances should be applied by analogy to other nitrosamines.

In case of identification of other nitrosamines, this should be forthwith reported to the competent authorities, together with a toxicology assessment of the impurity, a clinical assessment for the exposed patients, a root cause analysis and a corrective action plan (e.g. changes to the manufacturing process).

<u>Considerations on monitoring of exposed patients</u>

The above stated very small theoretical risk has to be balanced against the risks of measures to monitor patients such as colonoscopy or gastroscopy which may exceed the theoretical excess cancer risk. For example, a recent review has estimated risks of perforation of 4 per 10,000 (95% confidence

interval, 2-5) and major haemorrhage of 8 per 10,000 (95% confidence interval, 5-14) with screening colonoscopy (Lin et al. JAMA 2016). In addition, advancing age, comorbidity and use of anticoagulants were found to be strongly associated with both gastrointestinal and non-gastrointestinal complications. Furthermore, the target organ(s) of NDMA/NDEA toxicity in humans are still not sufficiently clear.For these reasons, CHMP could not identify cancer screening methods that patients would benefit from.

Overall, taking into account the available data discussed above, the benefit risk balance of medicines containing a sartan with a tetrazole ring remains positive subject to the conditions outlined below.

5. Condition(s) to the marketing authorisations

The marketing authorisation holder(s) shall complete the below conditions, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

<table>
<tr><th>Conditions to the MA</th><th>Due date</th></tr>
<tr><td>The MAH must ensure that the manufacturing processes of the drug substances used for their drug products are reviewed for the potential risk of formation of N-nitrosamines and changed as necessary to minimise nitrosamine contamination as much as possible.</td><td>Within 2 years after Commission Decision.</td></tr>
<tr><td>For all N-nitrosamines, the MAH must ensure a control strategy is in place in drug substance batches used for their drug products.</td><td>At the time of Commission Decision.</td></tr>
<tr><td>For N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), the MAH must introduce the following specifications for the drug substance:

1) Limits for NDMA and NDEA outlined below should be implemented for a transitional period of 2 years:
<table>
<tr><th>Drug substance*</th><th>Max. daily dose (mg)</th><th>NDEA Limit in ng/day</th><th>NDEA Limit in ppm in API</th><th>NDMA Limit in ng/day</th><th>NDMA Limit in ppm in API</th></tr>
<tr><td>Valsartan</td><td>320</td><td>26.5</td><td>0.082</td><td>96.0</td><td>0.300</td></tr>
<tr><td>Losartan</td><td>150</td><td>26.5</td><td>0.177</td><td>96.0</td><td>0.640</td></tr>
<tr><td>Olmesartan</td><td>40</td><td>26.5</td><td>0.663</td><td>96.0</td><td>2.400</td></tr>
<tr><td>Irbesartan</td><td>300</td><td>26.5</td><td>0.088</td><td>96.0</td><td>0.320</td></tr>
<tr><td>Candesartan</td><td>32</td><td>26.5</td><td>0.820</td><td>96.0</td><td>3.000</td></tr>
</table>
* These limits are not applicable for batches where more than one of the above N-nitrosamines has been identified simultaneously; such batches should be rejected.

2) After the transitional period of 2 years, a limit for NDMA and NDEA of maximum 0.03 ppm should be implemented.</td><td>At the time of Commission Decision

Within 2 years after Commission Decision.</td></tr>
</table>

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